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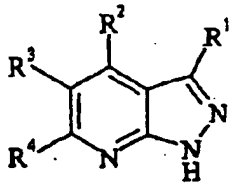
(54) Title: PYRAZOLOPYRIDINE DERIVATIVES



(I)

(57) Abstract: Certain compounds of formula (I), or a salt thereof, or a solvate thereof, wherein R_1, R_2, R_3 and R_4 are as defined in the specification, a process for the preparation of such compounds, a pharmaceutical composition comprising such compounds and the use of such compounds in medicine. For the treatment of conditions associated with a need for inhibition of GSK-3 such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Picks's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solidary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency.

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PYRAZOLOPYRIDINE DERIVATIVES

This invention relates to novel compounds, in particular to novel pyrazolopyridine derivatives, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds in medicine.

GSK-3 is a serine/threonine protein kinase composed of two isoforms (α and β) which are encoded by distinct genes. GSK-3 is one of several protein kinases which phosphorylates glycogen synthase (GS) (Embi *et al., Eur. J. Biochem.*, (107), 519-527, (1980)). The α and β isoforms have a monomeric structure and are both found in mammalian cells. Both isoforms phosphorylate muscle glycogen synthase (Cross *et al.*, *Biochemical Journal*, (303), 21-26, (1994)) and these two isoforms show good homology between species (*e.g.* human and rabbit GSK-3α are 96% identical).

Type II diabetes (or Non-Insulin Dependent Diabetes Mellitus, NIDDM) is a multifactorial disease. Hyperglycaemia is due to insulin resistance in the liver, muscle and other tissues coupled with inadequate or defective secretion of insulin from pancreatic islets. Skeletal muscle is the major site for insulin-stimulated glucose uptake and in this tissue, glucose removed from the circulation is either metabolised through glycolysis and the TCA cycle, or stored as glycogen. Muscle glycogen deposition plays the more important role in glucose homeostasis and Type II diabetic subjects have defective muscle glycogen storage.

The stimulation of glycogen synthesis by insulin in skeletal muscle results from the dephosphorylation and activation of glycogen synthase (Villar-Palasi C. and Larner J., *Biochim. Biophys. Acta.*, (39), 171-173, (1960), Parker P.J. *et al., Eur. J. Biochem.*, (130), 227-234, (1983) and Cohen P., *Biochem. Soc. Trans.*, (21), 555-567, (1993)). The phosphorylation and dephosphorylation of GS are mediated by specific kinases and phosphatases. GSK-3 is responsible for phosphorylation and deactivation of GS, while glycogen bound protein phosphatase 1 (PP1G) dephosphorylates and activates GS. Insulin both inactivates GSK-3 and activates PP1G (Srivastava A.K. and Pandey S.K., *Mol. and Cellular Biochem.*, (182), 135-141, (1998)).

Chen *et al.* (*Diabetes*, (43), 1234-1241, (1994)) found that there was no difference in the mRNA abundance of PP1G between patients with Type II diabetes and control patients, suggesting that an increase in GSK-3 activity might be important in Type II

diabetes. It has also recently been demonstrated that GSK-3 is overexpressed in Type II diabetic muscle and that an inverse correlation exists between skeletal muscle GSK-3α activity and insulin action (Nikoulina *et al.*, *Diabetes*, (49), 263-271, (2000)). Overexpression of GSK-3β and constitutively active GSK-3β(S9A, S9E) mutants in HEK-293 cells resulted in suppression of glycogen synthase activity (Eldar-Finkelman *et al.*, *PNAS*, (93), 10228-10233, (1996)) and overexpression of GSK-3β in CHO cells, expressing both insulin receptor and insulin receptor substrate 1 (IRS-1), resulted in an impairment of insulin action (Eldar-Finkelman and Krebs, *PNAS*, (94), 9660-9664, (1997)). Recent evidence for the involvement of elevated GSK-3 activity and the development of insulin resistance and type II diabetes in adipose tissue has emerged from studies undertaken in diabetes and obesity prone C57BL/6J mice (Eldar-Finkelman *et al.*, *Diabetes*, (48), 1662-1666, (1999)).

GSK-3 has been shown to phosphorylate other proteins *in vitro* including the eukaryotic initiation factor eIF-2B at $Serine^{540}$ (Welsh *et al.*, *FEBS Letts.*, (421), 125-130, (1998)). This phosphorylation results in an inhibition of eIF-2B activity and leads to a reduction in this key regulatory step of translation. In disease states, such as diabetes, where there is elevated GSK-3 activity this could result in a reduction of translation and potentially contribute to the pathology of the disease.

Several aspects of GSK-3 functions and regulation in addition to modulation of glycogen synthase activity indicate that inhibitors of this enzyme may be effective in treatment of disorders of the central nervous system. GSK-3 activity is subject to inhibitory phosphorylation by PI 3 kinase-mediated or Wnt-1 class-mediated signals that can be mimicked by treatment with lithium, a low mM inhibitor of GSK-3 (Stambolic V., Ruel L. and Woodgett J.R., *Curr. Biol.*, (6), 1664-8, (1996)).

GSK-3 inhibitors may be of value as neuroprotectants in treatment of acute stroke and other neurotraumatic injuries. Roles for PI 3-kinase signalling through PKB/akt to promote neuronal cell survival are well established, and GSK-3 is one of a number of PKB/akt substrates to be identified that can contribute to the inhibition of apoptosis via this pathway (Pap and Cooper, *J. Biol. Chem.*, (273), 19929-19932, ((1998)). Evidence suggests that astrocytic glycogen can provide an alternative energy source to facilitate neuronal survival under conditions of glucose deprivation (for example, see Ransom B.R. and Fern R., *Glia*, (21), 134-141, (1997) and references therein). Lithium is known to

protect cerebellar granule neurons from death (D'Mello *et al.*, *Exp. Cell Res.*, (211), 332-338, (1994) and Volonte *et al.*, *Neurosci. Letts.*, (172), 6-10, (1994)) and chronic lithium treatment has demonstrable efficacy in the middle cerebral artery occlusion model of stroke in rodents (Nonaka and Chuang, *Neuroreport*, (9), 2081-2084, (1998)). Wnt-induced axonal spreading and branching in neuronal culture models has been shown to correlate with GSK-3 inhibition (Lucas and Salinas, *Dev. Biol.*, (192), 31-44, (1997)) suggesting additional value of GSK-3 inhibitors in promoting neuronal regeneration following neurotraumatic insult.

Tau and β-catenin, two known *in vivo* substrates of GSK-3, are of direct relevance in consideration of further aspects of the value of GSK-3 inhibitors in relation to treatment of chronic neurodegenerative conditions. Tau hyperphosphorylation is an early event in neurodegenerative conditions such as Alzheimer's disease (AD), and is postulated to promote microtubule disassembly. Lithium has been reported to reduce the phosphorylation of tau, enhance the binding of tau to microtubules, and promote microtubule assembly through direct and reversible inhibition of glycogen synthase kinase-3 (Hong M., Chen D.C., Klein P.S. and Lee V.M., *J. Biol. Chem.*, (272), 25326-32, (1997). β-catenin is phosphorylated by GSK-3 as part of a tripartite complex with axin, resulting in β-catenin being targetted for degradation (Ikeda *et al.*, *J. EMBO.*, (17), 1371-1384, (1998)). Inhibition of GSK-3 activity is a key mechanism by which cytosolic levels of catenin are stabilised and hence promote β-catenin-LEF-1/TCF transcriptional activity (Eastman, Grosschedl, *Curr. Opin. Cell. Biol.*, (11), 233, (1999)). Rapid onset AD mutations in presenilin-1 (PS-1) have been shown to decrease the cytosolic β-catenin pool in transgenic mice. Further evidence suggests that such a reduction in available β-catenin may increase neuronal sensitivity to amyloid mediated death through inhibition of β-catenin-LEF-1/TCF transcriptional regulation of neuroprotective genes (Zhang *et al.*, *Nature*, (395), 698-702, (1998)). A likely mechanism is suggested by the finding that mutant PS-1 protein confers decreased inactivation of GSK-3 compared with normal PS-1 (Weihl C.C., Ghadge G.D., Kennedy S.G., Hay N., Miller R.J. and Roos R.P., *J. Neurosci.*, (19), 5360-5369, (1999)).

International Patent Application Publication Number WO 97/41854 (University of Pennsylvania) discloses that an effective drug for the treatment of manic depression is

lithium, but that there are serious drawbacks associated with this treatment. Whilst the precise mechanism of action of this drug for treatment of manic depression remains to be fully defined, current models suggest that inhibition of GSK-3 is a relevant target that contributes to the modulation of AP-1 DNA binding activity observed with this compound (see Manji *et al., J. Clin. Psychiatry*, (60) (suppl 2), 27-39, (1999) for review).

GSK-3 inhibitors may also be of value in treatment of schizophrenia. Reduced levels of β-catenin have been reported in schizophrenic patients (Cotter D., Kerwin R., al-Sarraji S., Brion J.P., Chadwich A., Lovestone S., Anderton B., and Everall I., *Neuroreport*, (9), 1379-1383, (1998)) and defects in pre-pulse inhibition to startle response have been observed in schizophrenic patients (Swerdlow *et al., Arch. Gen. Psychiat.*, (51), 139-154, (1994)). Mice lacking the adaptor protein dishevelled-1, an essential mediator of Wnt-induced inhibition of GSK-3, exhibit both a behavioural disorder and defects in pre-pulse inhibition to startle response (Lijam N., Paylor R., McDonald M.P., Crawley J.N., Deng C.X., Herrup K., Stevens K.E., Maccaferri G., McBain C.J., Sussman D.J., and Wynshaw-Boris A., *Cell*, (90), 895-905, (1997)). Together, these findings implicate deregulation of GSK-3 activity as contributing to schizophrenia. Hence, small molecule inhibitors of GSK-3 catalytic activity may be effective in treatment of this mood disorder.

The finding that transient β-catenin stabilisation may play a role in hair development (Gat *et al., Cell*, (95), 605-614, (1998)) suggests that GSK-3 inhibitors could be used in the treatment of baldness.

Studies on fibroblasts from the GSK-3β knockout mouse (Hoeflich K.P. *et al., Nature*, (406), 86-90, (2000)) support a role for this kinase in positively regulating the activity of NFkB. This transcription factor mediates cellular responses to a number of inflammatory stimuli. Therefore, pharmacologic inhibition of GSK-3 may be of use in treating inflammatory disorders through the negative regulation of NFkB activity.

The compounds of the present invention are pyrazolopyridine derivatives. Other pyrazolopyridine derivatives have been described previously for use in alternative medicinal applications. For example, International Patent Application Publication Numbers WO 97/23480 and WO 98/43962 describe various fused heterocyclic compounds, which may include pyrazolopyridazines, which are useful as antagonists of the $\alpha_v\beta_3$-integrin and related cell surface adhesive protein receptors. Such compounds

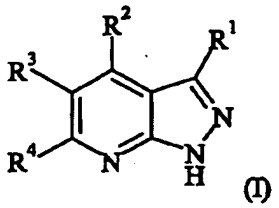
are indicated to be useful in the treatment of conditions such as angiogenic disorders, inflammation, bone degradation, cancer metastasis, diabetic retinopathy, thrombosis, restenosis, macular degeneration, and other conditions mediated by cell adhesion and/or cell migration and/or angiogenesis.

International Patent Application Publication Number WO 00/26211 describes various fused heterocyclic compounds, which may include pyrazolopyridines, which are useful in inhibiting thrombin and associated thrombotic occlusions. Such compounds are indicated to be useful in the treatment of conditions such as angina, myocardial infarction, thrombotic stroke, embolic stroke and the like.

International Patent Application Publication Number WO 02/24694 describes a series of pyrazolopyridine and pyrazolopyridazine derivatives as inhibitors of GSK-3.

We have now discovered that a series of pyrazolo[3,4-b]pyridines are potent and selective inhibitors of GSK-3. These compounds are indicated to be useful for the treatment and/or prophylaxis of conditions associated with a need for inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency.

Accordingly, in a first aspect, the present invention provides a compound of formula (I),



(I)

or a salt thereof, or a solvate thereof, wherein,

R^1 is $-NR^5COR^6$, $-NHCONHR^7$ or $-NHCO_2R^8$;

R^2 is H;

R^3 is H, halo, -CN, $-NO_2$, $-NH_2$, alkyl, alkenyl, $-C(OR^{10})=CHR^{13}$, $-NHCOR^{11}$, $-NHSO_2R^{12}$, $-CO_2R^{13}$, $-COCH_2R^{13}$, $-B(OR^{14})_2$, $-CONHR^{15}$, -SPh, heteroaryl or aryl wherein the aryl group may be optionally substituted by one or more halo substituents;

R^4 is H, cycloC_{3-8} alkyl, heterocyclyl, heteroaryl wherein the heteroaryl group may be optionally substituted by alkyl and di-alkylaminoalkyl; or aryl wherein the aryl group may be optionally substituted by one or more groups selected from halo, -OH, $-CF_3$, -CN, alkoxy and arylalkoxy, or may be fused to a heterocyclic ring to form a bicyclic group;

R^5 is H or alkyl;

R^6 is alkyl, alkenyl, cycloC_{3-8} alkyl, cycloC_{3-8} alkenyl, di-alkylaminoalkyl, arylalkyl, arylalkenyl, heterocyclyl wherein the heterocyclyl group may be optionally substituted by one or more groups selected from alkyl, arylalkyl and alkoxyalkyl; heterocyclylalkyl wherein the heterocyclyl may be optionally substituted by one or more groups selected from alkoxyalkyl, aryloxyalkyl, arylalkyl and alkyl; heteroarylalkyl wherein the heteroaryl may be optionally substituted by one or more groups selected from alkyl; heteroaryl wherein the heteroaryl may be optionally substituted by one or more groups selected from aryl and heteroaryl; aryl wherein the aryl group may be optionally substituted by heterocyclylalkyl and di-alkylaminoalkyl; alkoxyalkyl wherein the alkoxy group may be optionally substituted by alkoxy;

R^7 is alkyl or aryl wherein the aryl group may be optionally substituted by one or more groups selected from alkyl, alkoxy, -CN and $-CO_2R^9$;

R^8 is alkyl or arylalkyl; and

R^9 is alkyl;

R^{10} is alkyl;

R^{11} is alkyl, alkoxyalkyl, arylalkyl or aryl wherein the aryl group may be optionally substituted by one or more groups selected from halo; and

R^{12} is alkyl;

R^{13} is alkyl;

R^{14} is alkyl or two R^{14} groups together form a ring system which may be further substituted by one or more alkyl group(s);

R^{15} is di-alkylaminoalkyl;

with the proviso that when R^1 is $-NR^5COR^6$ wherein R^5 is H and R^6 is as hereinbefore defined, and R^2 and R^4 are H then R^3 is selected from H, halo, -CN, $-NO_2$, $-NH_2$, alkyl, alkenyl, $-C(OR^{10})=CHR^{13}$, $-NHCOR^{11}$, $-NHSO_2R^{12}$, $-CO_2R^{13}$, $-COCH_2R^{13}$, $-CONHR^{15}$ or –SPh.

Suitably, R^1 is $-NR^5COR^6$. More suitably, R^1 is –NHCOMe, $-NHCOPr^n$, $-NHCOPr^i$, $-N(Et)COPr^n$, $-NHCOBu^s$, $-NHCO(CH_2)_4$-thiomorpholin-4-yl, -NHCOcyclo-Propyl, -NHCOcyclo-Pentyl, -NHCO-4-(N-Me-Piperidyl), $-NHCO(CH_2)_3$-(4-Et-Piperazin-1-yl), $-NHCO(CH_2)_3NMe_2$, $-NHCO(CH_2)_2$(6-Me-Pyridin-3-yl), -NHCO-[3-(pyrid-2-yl)-Ph], -NHCO-[4-(CH_2(pyrrolidin-1-yl)-Ph], -NHCO-[6-(3-Pyridyl)-pyrid-3-yl], -NHCO-3-(N-CH_2Ph-Pyrrolidinyl), -NHCO-4-(N-$((CH_2)_2OMe)$-Piperidyl), $-NHCOCH(Me)(CH_2)_2$-(4-Et-piperazin-1-yl), $-NHCOCH_2$(N-$(CH_2)_2$OMe-Piperidin-4-yl), $-NHCOCH_2$(N-$(CH_2)_2$OPh-Piperidin-4-yl), $-NHCOCH_2$(N-CH_2Ph-Piperidin-4-yl), $-NHCOCH_2$(N-Et-Piperidin-4-yl), $-NHCOCH_2O(CH_2)_2OMe$, $-NHCOCH_2OMe$, $-NHCO(CH_2)_2$-morpholin-4-yl, $-NHCO(CH_2)_3$(pyrrolidin-1-yl), -NHCO-[4-(CH_2(piperidin-1-yl)-Ph], -NHCO-[4-(CH_2NEt_2)-Ph], -NHCO-4-(N-$(CH_2)_2$OEt-Piperidyl) or $-NHCOCH_2NMe_2$.

Suitably, R^1 is $-NHCONHR^7$. More suitably, R^1 is NHCONHEt, -NHCONH(2-Me-Ph), -NHCONH(2-MeO-Ph), -NHCONH(2-CN-Ph), or-NHCONH(2-CO_2Me-Ph).

Suitably, R^1 is $NHCO_2R^8$. More suitably, R^1 is $-NHCO_2Et$, $-NHCO_2Pr^i$ or $-NHCO_2CH_2Ph$.Most suitably, R^1 is –NHCOMe, $-NHCOPr^n$, $-NHCOPr^i$, $-N(Et)COPr^n$, $-NHCOBu^s$, $-NHCO(CH_2)_4$-thiomorpholin-4-yl, -NHCOcyclo-Propyl, -NHCOcyclo-

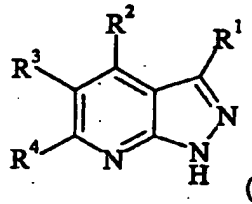
Pentyl, -NHCO-4-(N-Me-Piperidyl), -NHCO$(CH_2)_3$-(4-Et-Piperazin-1-yl), -NHCO$(CH_2)_3NMe_2$, -NHCONHEt, -NHCONH(2-Me-Ph), -NHCONH(2-MeO-Ph), -NHCONH(2-CN-Ph), -NHCONH(2-CO_2Me-Ph), -$NHCO_2$Et, -$NHCO_2Pr^i$, -$NHCO_2CH_2$Ph, -NHCO$(CH_2)_2$(6-Me-Pyridin-3-yl), -NHCO-[3-(pyrid-2-yl)-Ph], -NHCO-[4-(CH_2(pyrrolidin-1-yl)-Ph], -NHCO-[6-(3-Pyridyl)-pyrid-3-yl], -NHCO-3-(N-CH_2Ph-Pyrrolidinyl), -NHCO-4-(N-(($CH_2)_2$OMe)-Piperidyl), -NHCOCH(Me)$(CH_2)_2$-(4-Et-piperazin-1-yl), -$NHCOCH_2$(N-$(CH_2)_2$OMe-Piperidin-4-yl), -$NHCOCH_2$(N-$(CH_2)_2$OPh-Piperidin-4-yl), -$NHCOCH_2$(N-CH_2Ph-Piperidin-4-yl), -$NHCOCH_2$(N-Et-Piperidin-4-yl), -$NHCOCH_2O(CH_2)_2$OMe, -$NHCOCH_2$OMe, -NHCO$(CH_2)_2$-morpholin-4-yl, -NHCO$(CH_2)_3$(pyrrolidin-1-yl), -NHCO-[4-(CH_2(piperidin-1-yl)-Ph], -NHCO-[4-(CH_2NEt_2)-Ph], -NHCO-4-(N-$(CH_2)_2$OEt-Piperidyl) and -$NHCOCH_2NMe_2$.

Suitably, R^3 is H, halo, -CN, -NO_2 or alkyl. Suitably, R^3 is aryl wherein the aryl group may be optionally substituted by one or more halo substituents. Most suitably, R^3 is H, methyl, phenyl, bromo, chloro, iodo, cyano, pinacolboronato, -$CH_2CH{=}CH_2$, -$CH{=}CH_2$, -$C(OEt){=}CH_2$, 2-fluorophenyl, -COMe, 3-fluorophenyl, -NO_2, -NHCOMe, -$NHCOPr^i$, -$NHSO_2$Me, -NH_2, -NHCOPh, -NHCO(2,3-difluorophenyl), -$NHCOCH_2$Ph, -$NHCOCH_2$OMe, 3-pyridyl, -CO_2Et, -CONH$(CH_2)_2NMe_2$ and –SPh.

Suitably, R^4 is H. Suitably, R^4 is cycloC_{3-8} alkyl, heterocyclyl, heteroaryl wherein the heteroaryl group may be optionally substituted by alkyl and di-alkylaminoalkyl. Suitably, R^4 is aryl wherein the aryl group may be optionally substituted by one or more groups selected from halo, -OH, -CF_3, -CN, alkoxy and arylalkoxy, or may be fused to a heterocyclic ring to form a bicyclic group. Most suitably, R^4 is H, phenyl, 4-chlorophenyl, 3-trifluoromethylphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3,4-dihydroxyphenyl, 3,4-methylenedioxyphenyl, 4-benzyloxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-pyridyl, 3-chloro-4-hydroxyphenyl, 3-bromo-4-hydroxyphenyl, 2-thienyl, 2-furyl, 2-thiazolyl, 3-CN-Ph, 5-(CH_2NMe_2)-Furan-2-yl, 5-Me-Furan-2-yl and cyclo-Propyl.

Suitably, R^5 is H. Suitably, R^5 is alkyl.

In a preferred aspect of the present invention there is provided a subset of compounds of formula (I), of formula (IA),



(IA)

or a salt thereof, or a solvate thereof, wherein,

R^1 is $-NR^5COR^6$, $-NHCONHR^7$ or $-NHCO_2R^8$;

R^2 is H;

R^3 is H, halo, -CN, $-NO_2$, $-NH_2$, alkyl, alkenyl, $-C(OR^{10})=CHR^{13}$, $-NHCOR^{11}$, $-NHSO_2R^{12}$, $-CO_2R^{13}$, $-COCH_2R^{13}$, $-B(OR^{14})_2$, $-CONHR^{15}$, -SPh, heteroaryl or aryl wherein the aryl group may be optionally substituted by one or more halo substituents;

R^4 is H, cycloC_{3-8} alkyl, heterocyclyl, heteroaryl wherein the heteroaryl group may be optionally substituted by alkyl and di-alkylaminoalkyl; or aryl wherein the aryl group may be optionally substituted by one or more groups selected from halo, -OH, $-CF_3$, -CN, alkoxy and arylalkoxy, or may be fused to a heterocyclic ring to form a bicyclic group;

R^5 is H or alkyl;

R^6 is alkyl, cycloC_{3-8} alkyl, di-alkylaminoalkyl, heterocyclyl wherein the heterocyclyl group may be optionally substituted by one or more groups selected from alkyl, arylalkyl and alkoxyalkyl; heterocyclylalkyl wherein the heterocyclyl may be optionally substituted by one or more groups selected from alkoxyalkyl, aryloxyalkyl, arylalkyl and alkyl; heteroarylalkyl wherein the heteroaryl may be optionally substituted by one or more groups selected from alkyl; heteroaryl wherein the heteroaryl may be optionally substituted by one or more groups selected from aryl and heteroaryl; aryl wherein the aryl group may be optionally substituted by heterocyclylalkyl and di-alkylaminoalkyl; alkoxyalkyl wherein the alkoxy group may be optionally substituted by alkoxy;

R^7 is alkyl or aryl wherein the aryl group may be optionally substituted by one or more groups selected from alkyl, alkoxy, -CN and CO_2R^9;

R^8 is alkyl or arylalkyl;

R^9 is alkyl;

R^{10} is alkyl;

R^{11} is alkyl, alkoxyalkyl, arylalkyl or aryl wherein the aryl group may be optionally substituted by one or more groups selected from halo; and

R^{12} is alkyl;

R^{13} is alkyl;

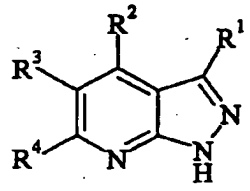
R^{14} is alkyl or two R^{14} groups together form a ring system which may be further substituted by one or more alkyl group(s);

R^{15} is di-alkylaminoalkyl;

with the proviso that when R^1 is $-NR^5COR^6$ wherein R^5 is H and R^6 is as hereinbefore defined, and R^2 and R^4 are H then R^3 is selected from H, halo, -CN, $-NO_2$, $-NH_2$, alkyl, alkenyl, $-C(OR^{10})=CHR^{13}$, $-NHCOR^{11}$, $-NHSO_2R^{12}$, $-CO_2R^{13}$, $-COCH_2R^{13}$ - $CONHR^{15}$ or –SPh.

Suitably R^3 is H, chloro, bromo, iodo, cyano, alkyl and aryl.

In a further preferred aspect of the present invention there is provided a subset of compounds of formula (I), of formula (IB),



(IB)

or a salt thereof, or a solvate thereof, wherein,

R^1 is –NHCOMe, $-NHCOPr^n$, $-NHCOPr^i$, $-N(Et)COPr^n$, $-NHCOBu^s$, $-NHCO(CH_2)_4$-thiomorpholin-4-yl, -NHCOcyclo-Propyl, -NHCOcyclo-Pentyl, -NHCO-4-(N-Me-Piperidyl), $-NHCO(CH_2)_3$-(4-Et-Piperazin-1-yl), $-NHCO(CH_2)_3NMe_2$, -NHCONHEt, -NHCONH(2-Me-Ph), -NHCONH(2-MeO-Ph), -NHCONH(2-CN-Ph), $-NHCONH(2-CO_2Me-Ph)$, $-NHCO_2Et$, $-NHCO_2Pr^i$, $-NHCO_2CH_2Ph$, $NHCO(CH_2)_2$(6-Me-Pyridin-3-yl), NHCO-[3-(pyrid-2-yl)-Ph], NHCO-[4-(CH_2(pyrrolidin-1-yl)-Ph],

NHCO-[6-(3-Pyridyl)-pyrid-3-yl], NHCO-3-(N-CH_2Ph-Pyrrolidinyl), NHCO-4-(N-((CH_2)$_2$OMe)-Piperidyl), NHCOCH(Me)(CH_2)$_2$-(4-Et-piperazin-1-yl), NHCOCH_2(N-(CH_2)$_2$OMe-Piperidin-4-yl), NHCOCH_2(N-(CH_2)$_2$OPh-Piperidin-4-yl), NHCOCH_2(N-CH_2Ph-Piperidin-4-yl), NHCOCH_2(N-Et-Piperidin-4-yl), NHCOCH_2O(CH_2)$_2$OMe, NHCOCH_2OMe, -NHCO(CH_2)$_2$-morpholin-4-yl, -NHCO(CH_2)$_3$(pyrrolidin-1-yl), -NHCO-[4-(CH_2(piperidin-1-yl)-Ph], -NHCO-[4-(CH_2NEt_2)-Ph], -NHCO-4-(N-(CH_2)$_2$OEt-Piperidyl) and -NHCOCH_2NMe_2;

R^2 is H;

R^3 is H, methyl, phenyl, bromo, chloro, iodo, cyano, pinacolboronato, -CH_2CH=CH_2, -CH=CH_2, -C(OEt)=CH_2, 2-fluorophenyl, -COMe, 3-fluorophenyl, -NO_2, -NHCOMe, -NHCOPr^i, -NHSO_2Me, -NH_2, -NHCOPh, -NHCO(2,3-difluorophenyl), -NHCOCH_2Ph, -NHCOCH_2OMe, 3-pyridyl, -CO_2Et, -CONH(CH_2)$_2$NMe_2, and -SPh;

R^4 is H, phenyl, 4-chlorophenyl, 3-trifluoromethylphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3,4-dihydroxyphenyl, 3,4-methylenedioxyphenyl, 4-benzyloxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-pyridyl, 3-chloro-4-hydroxyphenyl, 3-bromo-4-hydroxyphenyl and 2-thienyl, 2-furyl 2-thiazolyl, 3-CN-Ph, 5-(CH_2NMe_2)-Furan-2-yl, 5-Me-Furan-2-yl and cyclopropyl;

with the proviso that when R^1 is -NHCOMe, -NHCOPr^n, -NHCOPr^i, -NHCOBu^s, -NHCO(CH_2)$_4$-thiomorpholin-4-yl, -NHCOcyclo-Propyl, -NHCOcyclo-Pentyl, -NHCO-4-(N-Me-Piperidyl), -NHCO(CH_2)$_3$-(4-Et-Piperazin-1-yl), -NHCO(CH_2)$_3$NMe_2, NHCO(CH_2)$_2$(6-Me-Pyridin-3-yl), NHCO-[3-(pyrid-2-yl)-Ph], NHCO-[4-(CH_2(pyrrolidin-1-yl)-Ph], NHCO-[6-(3-Pyridyl)-pyrid-3-yl], NHCO-3-(N-CH_2Ph-Pyrrolidinyl), NHCO-4-(N-((CH_2)$_2$OMe)-Piperidyl), NHCOCH(Me)(CH_2)$_2$-(4-Et-piperazin-1-yl), NHCOCH_2(N-(CH_2)$_2$OMe-Piperidin-4-yl), NHCOCH_2(N-(CH_2)$_2$OPh-Piperidin-4-yl), NHCOCH_2(N-CH_2Ph-Piperidin-4-yl), NHCOCH_2(N-Et-Piperidin-4-yl), NHCOCH_2O(CH_2)$_2$OMe, NHCOCH_2OMe, -NHCO(CH_2)$_2$-morpholin-4-yl, -NHCO(CH_2)$_3$(pyrrolidin-1-yl), -NHCO-[4-(CH_2(piperidin-1-yl)-Ph], -NHCO-[4-(CH_2NEt_2)-Ph], -NHCO-4-(N-(CH_2)$_2$OEt-Piperidyl) and -NHCOCH_2NMe_2; and R^2 and R^4 are H, then R^3 is selected from H, methyl, bromo, chloro, iodo, cyano, -CH_2CH=CH_2, -CH=CH_2, -C(OEt)=CH_2, -COMe, -NO_2, -NHCOMe, -NHCOPr^i, -

$NHSO_2Me$, $-NH_2$, -NHCOPh, -NHCO(2,3-difluorophenyl), $-NHCOCH_2Ph$ - $NHCOCH_2OMe$, CO_2Et, $CONH(CH_2)_2NMe_2$, and –SPh.

Particularly preferred compounds of formula (I) which are of special interest as agents useful in the treatment and/or prophylaxis of conditions associated with a need for inhibition of GSK-3 are provided in Table 1 below.

Certain compounds of formula (I) may contain chiral atoms and/or multiple bonds, and hence may exist in one or more stereoisomeric forms. The present invention encompasses all of the isomeric forms of the compounds of formula (I) whether as individual isomers or as mixtures of isomers, including geometric isomers and racemic modifications.

As used herein the term "alkyl" as a group or part of a group refers to a straight or branched chain saturated aliphatic hydrocarbon radical containing 1 to 12 carbon atoms, suitably 1 to 6 carbon atoms. Such alkyl groups in particular include methyl ("Me"), ethyl ("Et"), n-propyl ("Pr^n"), *iso*-propyl ("Pr^i"), n-butyl ("Bu^n"), *sec*-butyl ("Bu^s"), *tert*-butyl ("Bu^t"), pentyl and hexyl. Where appropriate, such alkyl groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl and di-C_{1-6} alkylamino.

As used herein the term "alkenyl" as a group or part of a group refers to a straight or branched chain mono- or poly-unsaturated aliphatic hydrocarbon radical containing 2 to 12 carbon atoms, suitably 2 to 6 carbon atoms. References to "alkenyl" groups include groups which may be in the E- or Z-form or mixtures thereof. Such alkenyl groups in particular include ethenyl, propenyl, butenyl, pentenyl and hexenyl. Where appropriate, such alkenyl groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{1-6} alkyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl and di-C_{1-6} alkylamino.

As used herein the term "alkynyl" refers to hydrocarbon groups of either straight or branched configuration with one or more carbon-carbon triple bonds which may occur at any stable point in the chain, containing 3 to 12 carbon atoms, suitably 3 to 6 carbon atoms. Such alkynyl groups in particular include propynyl, butynyl and pentynyl. Where appropriate, such alkynyl groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, aryl and di-C_{1-6} alkylamino.

As used herein, the term "alkoxy" as a group or part of a group refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Such alkoxy groups in particular include methoxy, ethoxy, n-propoxy, *iso*-propoxy, n-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy. Where appropriate, such alkoxy groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, aryl and di-C_{1-6} alkylamino.

As used herein, the term "aryl" as a group or part of a group refers to a carbocyclic aromatic radical. Suitably such aryl groups are 5-6 membered monocyclic groups or 8-10 membered fused bicyclic groups, especially phenyl ("Ph"), biphenyl and naphthyl, particularly phenyl. Such aryl groups may be optionally substituted with one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, $-NO_2$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy and di-C_{1-6} alkylamino.

As used herein, the term "heteroaryl" as a group or part of a group refers to stable heterocyclic aromatic single and fused rings containing one or more hetero atoms independently selected from nitrogen, oxygen and sulfur. A fused heteroaryl ring system may include carbocyclic rings and need include only one heteroaryl ring. Such heteroaryl groups include furyl, thienyl, pyridazinyl, pyridyl, quinolinyl, indolyl, thiazolyl, benzoxazolyl, and benzothiazolyl. Each ring may be optionally substituted with one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-NO_2$, $-OCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl, heteroaryl, and di-C_{1-6} alkylamino.

As used herein, the terms "heterocyclyl" and "heterocyclic" as a group or part of a group refer to stable heterocyclic non-aromatic single and fused rings containing one or more hetero atoms independently selected from nitrogen, oxygen and sulfur. A fused heterocyclyl ring system may include carbocyclic rings and need include only one heterocyclic ring. Such heterocyclyl groups include piperazinyl, piperidinyl and morpholinyl. Each ring may be optionally substituted with one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-NO_2$, $-OCF_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl, heteroaryl, and di-C_{1-6} alkylamino.

As used herein the terms "halo" include iodo, bromo, chloro or fluoro, suitably bromo, chloro and fluoro, especially bromo and chloro.

Composite terms such as "alkoxyalkyl" and "arylalkyl" refer to substituents comprising two interlinked groups, with the group named latterly in the term being the linking group, so that "alkoxyalkyl" means -(alkyl)-(alkoxy) whilst "arylalkyl" means -(alkyl)-(aryl).

The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, *inter alia*, having a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula (I) or its salt or solvate.

One preferred pharmaceutically acceptable form is the crystalline form, including such form in pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Suitable salts are pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable salts include the acid addition salts with the conventional pharmaceutical acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.

Suitable pharmaceutically acceptable salts include salts of acidic moieties of the compounds of formula (I) when they are present, for example salts of carboxy groups or phenolic hydroxy groups.

Suitable salts of acidic moieties include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxyalkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine,

glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

Suitable solvates are pharmaceutically acceptable solvates.

Suitable pharmaceutically acceptable solvates include hydrates.

For the avoidance of doubt when used herein the term "diabetes" includes diabetes mellitus, especially Type 2 diabetes, and conditions associated with diabetes mellitus.

The term "conditions associated with diabetes" includes those conditions associated with the pre-diabetic state, conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus.

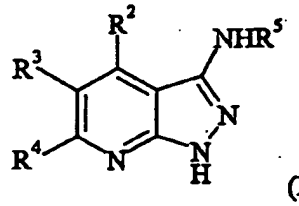
The term "conditions associated with the pre-diabetic state" includes conditions such as insulin resistance, impaired glucose tolerance and hyperinsulinaemia.

The term "conditions associated with diabetes mellitus itself" includes hyperglycaemia, insulin resistance and obesity. Further conditions associated with diabetes mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance.

The term "complications associated with diabetes mellitus" includes renal disease, especially renal disease associated with Type II diabetes, neuropathy and retinopathy. Renal diseases associated with Type II diabetes include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

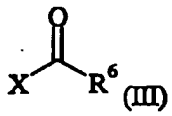
The term "neurotraumatic diseases" includes both open or penetrating head trauma, such as caused by surgery, or a closed head trauma injury, such as caused by an injury to the head region, ischaemic stroke including acute stroke, particularly to the brain area, transient ischaemic attacks following coronary by-pass and cognitive decline following other transient ischaemic conditions.

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) wherein R^1 is $-NR^5COR^6$ and wherein R^2, R^3, R^4, R^5 and R^6 are as hereinbefore defined, or a salt and/or solvate thereof, which process comprises reacting a compound of formula (II),



(II)

wherein R^2, R^3, R^4 and R^5 are as defined in relation to formula (I) with a compound of formula (III),



(III)

wherein R^6 is as defined in relation to formula (I) and X is a suitable leaving group and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate derivative of the compound so formed.

Suitably X is chloro. It will be appreciated that compounds of formula (III) may also include related carboxylic acid anhydrides.

It will be appreciated that where R^5 is alkyl, compounds of formula (II) may be prepared from other compounds of formula (II) where R^5 is H, by conventional procedures, such as acylation and subsequent reduction.

The reaction between the compounds of formulae (II) and (III) is carried out in a suitable solvent, under conventional conditions, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. A suitable solvent is pyridine. Suitable reaction temperatures include those in the range of 20°C to 220°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 0.1 to 72 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, a compound of formula (III), such as acetic anhydride, is added to a solution of the compound of formula (II) in pyridine, with stirring. The reaction mixture is heated under reflux for 16 hours, allowed to cool to ambient temperature and then treated with a suitable acid, such as hydrochloric acid. The resulting solid is isolated by filtration, washed with a suitable solvent, such as water, and recrystallised from a suitable solvent, such as dimethylformamide, to afford the desired compound of formula (I).

In a further preferred aspect, to a compound of formula (II) in pyridine is added a compound of formula (III), such as butyrylchloride. The reaction mixture is heated under reflux, with stirring, for 16 hours. Upon cooling the solvent is removed *in vacuo*, to afford a residue which is taken up in a suitable solvent, such as methanol, and passed through an SCX cartridge with a suitable solvent, such as methanol. Product material is eluted using a suitable solvent such as methanolic ammonia solution. Further purification using silica chromotagraphy with one or more suitable solvents, such as 10% methanol in dichloromethane, affords a residue which is triturated with a suitable solvent, such as dichloromethane, to afford the desired compound of formula (I).

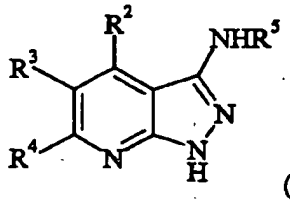
In still a further preferred aspect, to a stirred solution of a compound of formula (II) in dry pyridine is added a compound of formula (III), such as cyclopropyl carbonyl chloride. The solution is heated under reflux with stirring for 1 hour, allowed to cool and the resulting mixture concentrated. The resulting residue is triturated with dichloromethane/methanol to afford the desired compound of formula (I).

In still a further preferred aspect, a compound of formula (III), such as isobutyryl chloride, is added to a solution of a compound of formula (II) in hot pyridine. The reaction mixture is stirred under reflux for 55 hours, allowed to cool, and the solvent removed *in vacuo*. The resulting residue is purified using silica gel chromatography with one or more suitable solvents, such as 10% methanol/dichloromethane, to afford the desired compound of formula (I).

In still a further preferred aspect, a compound of formula (II) is added to a stirred solution of a compound of formula (III), such as 4-(4-ethylpiperazin-1-yl)-butyryl chloride hydrochloride salt, in dry pyridine at room temperature under an argon atmosphere. The mixture is heated under reflux for 16 hours, allowed to cool, and water is added to the resulting solution, which is subsequently evaporated to dryness. Ethanol is added to the

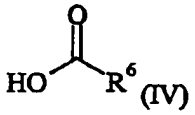
residue and the resulting solution is evaporated to dryness. The residue is dissolved in a suitable solvent, such as dimethylformamide, and purified by preparative HPLC with one or more suitable solvents, such as a gradient of 10-90% acetonitrile (0.1% trifluoroacetic acid) in water (0.1% trifluoroacetic acid). The resulting product is passed through an SCX cartridge with a suitable solvent, such as methanol. Product material is eluted using a suitable solvent such as methanolic ammonia solution. The resulting solution is then evaporated to dryness, dissolved in methanol and treated with a suitable acid, such as maleic acid to give the desired compound of formula (I).

Compounds of formula (I) wherein R^1 is $-NR^5COR^6$ and wherein R^2, R^3, R^4, R^5 and R^6 are as hereinbefore defined, or a salt and/or solvate thereof, may also be prepared by reaction of a compound of formula (II),



(II)

wherein R^2, R^3, R^4 and R^5 are as defined in relation to formula (I) with a compound of formula (IV),



(IV)

wherein R^6 is as defined in relation to formula (I), in the presence of a suitable coupling reagent and a suitable base and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate derivative of the compound so formed;

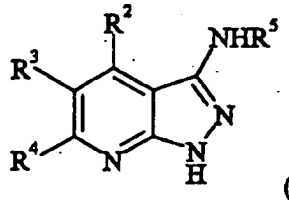
thereby constituting a further aspect of the present invention.

The reaction between the compounds of formulae (II) and (IV) is carried out in a suitable solvent, under conventional conditions, at a suitable temperature, providing a

suitable rate of formation of the required product, over a suitable reaction time. A suitable coupling reagent is O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate. A suitable base is a tertiary amine. A suitable solvent is dimethylformamide. Suitable reaction temperatures include those in the range of 20°C to 60°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 12 to 72 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, to a stirred solution of a compound of formula (II) in dimethylformamide is added a compound of formula (II), such as 3-methylbutyric acid, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and a suitable base, such as triethylamine. The solution is stirred under ambient conditions for 16 hours. Additional O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and base are added to the reaction mixture and it is allowed to stir for a further 3 hours. The resulting mixture is concentrated *in vacuo* to afford a residue, which is passed through an SCX cartridge with a suitable eluant such as methanol. Typically, the mixture is further purified by preparative HPLC using one or more suitable solvents, such as a gradient of 10-90% acetonitrile containing 0.01% trifluoroacetic acid. The solvent is removed from the resulting solution to afford the desired compound of formula (I).

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) wherein R^1 is –NHCONHR^7 and wherein R^2, R^3, R^4 and R^7 are as hereinbefore defined, or a salt and/or solvate thereof, which process comprises reacting a compound of formula (II),



(II)

wherein R^2, R^3, R^4 are as defined in relation to formula (I) and R^5 is H, with a compound of formula (V),

$$R^7—NCO \quad (V)$$

wherein R^7 is as defined in relation to formula (I) and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

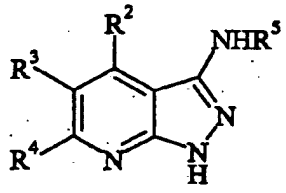
(iii) preparing an appropriate derivative of the compound so formed.

The reaction between the compounds of formulae (II) and (V) is carried out in a suitable solvent, under conventional conditions, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. A suitable solvent is pyridine. Suitable reaction temperatures include those in the range of 20°C to 220°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 12 to 48 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, to a stirred solution of a compound of formula (II) in dry pyridine is added a compound of formula (III) such as ethyl isocyanate. After 18 hours, a suitable acid, such as hydrochloric acid, is added to the reaction mixture. The resulting precipitate is isolated by filtration to afford the desired compound of formula (I).

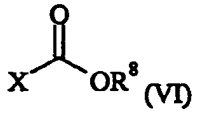
According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) wherein R^1 is $-NHCO_2R^8$ and wherein

R^2, R^3, R^4 and R^8 are as hereinbefore defined, or a salt and/or solvate thereof, which process comprises reacting a compound of formula (II),



(II)

wherein R^2, R^3, R^4 are as defined in relation to formula (I) and R^5 is H, with a compound of formula (VI),



(VI)

wherein R^8 is as defined in relation to formula (I) and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

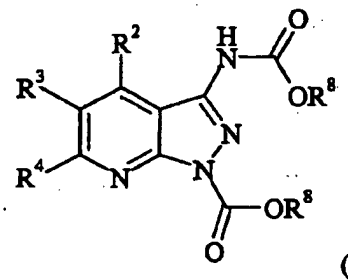
(iii) preparing an appropriate derivative of the compound so formed.

The reaction between the compounds of formulae (II) and (VI) is carried out in a suitable solvent, under conventional conditions, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. It will be appreciated that the reaction between a compound of formula (II) and a compound of formula (VI) may be assisted by the presence of a suitable catalyst such as 4-(dimethylaminopyridine). Suitable solvents include pyridine and tetrahydrofuran. Suitable reaction temperatures include those in the range of 20°C to 220°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 12 to 48 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, to a compound of formula (II) in dry pyridine is added 4-(dimethylamino)pyridine and a compound of formula (VI), such as ethyl chloroformate. The reaction mixture is heated in an argon atmosphere, under reflux, for 16 hours. Upon cooling, the reaction mixture is evaporated *in vacuo* to afford a residue, which is triturated with a suitable solvent, such as dichloromethane. The resulting solid is purified by silica gel chromatography using one or more suitable solvents, such as 5% methanol/dichloromethane to afford the desired compound of formula (I).

In a still further preferred aspect, to a stirred suspension of a compound of formula (II) in dry tetrahydrofuran is added 4-(dimethylamino)pyridine and a compound of formula (VI), such as isopropyl chloroformate. The reaction mixture is stirred for 16 hours and subsequently concentrated *in vacuo*. The resulting solid is purified by silica gel chromatography with one or more suitable solvents, such as 10% acetonitrile/dichloromethane, to afford the desired compound of formula (I).

Compounds of formula (I) wherein R^1 is $-NHCO_2R^8$ and wherein R^2, R^3, R^4 and R^8 are as hereinbefore defined, or a salt and/or solvate thereof, may also be prepared by reaction of a compound of formula (VII),



(VII)

wherein R^2, R^3, R^4 and R^8 are as defined in relation to formula (I) with an amine and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate derivative of the compound so formed;

thereby constituting a further aspect of the present invention.

The reaction between the compound of formula (VII) and an amine is carried out optionally in a suitable solvent, under conventional conditions, at a suitable temperature,

providing a suitable rate of formation of the required product, over a suitable reaction time. Suitably the reaction is carried out using the amine as a solvent. Suitable amines include primary and secondary amines. Suitable reaction temperatures include those in the range of 20°C to 100°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 12 to 48 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, the compound of formula (VII) is dissolved in a suitable amine, such as piperidine, and stirred for 12 hours under ambient conditions. The amine is then removed *in vacuo* to afford a residue which is typically purified using silica gel chromatography with one or more suitable solvents, such as a solvent gradient of 10-30% acetonitrile/dichloromethane, to afford the desired compound of formula (I).

The above-mentioned conversions of a compound of formula (I) into another compound of formula (I) include any conversion, which may be effected using conventional procedures, but in particular the said conversions include any combination of:

(i) converting one group R^1 into another group R^1;

(ii) converting one group R^3 into another group R^3;

(iii) converting one group R^4 into another group R^4.

The above-mentioned conversions (i), (ii) and (iii) may be carried out using any appropriate method under conditions determined by the particular groups chosen.

Suitable conversions of one group R^3 into another group R^3, as in conversion (ii) above, include:

(a) converting a group R^3 which represents halo, such as bromo, into another group R^3 which represents H. Such a conversion may be performed using an appropriate dehalogenation procedure, for example, by treating a compound of formula (I) wherein R^3 is halo, such as bromo, with a suitable base, such as sodium carbonate, in the presence of a suitable catalyst, such as $Pd(PPh_3)_4$.

(b) converting a group R^3 which represents halo, such as bromo, into another group R^3 which represents alkyl, alkenyl or $-C(OR^{10})=CHR^{13}$ wherein R^{10} and R^{13} are defined in relation to formula (I). Such a conversion may be performed using an appropriate alkylation or vinylation procedure, for example, by treating a compound of formula (I) wherein R^3 is halo, such as bromo, with a suitable reagent, such as an alkyl tin complex, for example (1-ethoxyvinyl) tributyltin, in the presence of a suitable catalyst, such as $Pd(PPh_3)_4$.

(c) converting a group R^3 which represents $-C(OR^{10})=CHR^{13}$ wherein R^{10} and R^{13} are defined in relation to formula (I), into another group R^3 which represents $-COCH_2R^{13}$ wherein R^{13} is defined in relation to formula (I). Such a conversion may be performed, for example, by treating a compound of formula (I) wherein R^3 is $-C(OR^{10})=CHR^{13}$ wherein R^{10} and R^{13} defined in relation to formula (I), with a suitable acid, such as hydrochloric acid, and thereafter, if necessary, treating the resulting product with an acid chloride or an acid anhydride, such as butyryl chloride.

(d) converting a group R^3 which represents $-NO_2$ into another group R^3 which represents $-NH_2$. Such a conversion may be performed using an appropriate hydrogenation procedure, for example, by treating a compound of formula (I) wherein R^3 is $-NO_2$ with a H_2 in the presence of a suitable catalyst, such as 10% Pd/C.

(e) converting a group R^3 which represents $-NH_2$ into another group R^3 which represents $-NHCOR^{11}$ or $-NHSO_2R^{12}$ wherein R^{11} and R^{12} are defined in relation to formula (I). Such a conversion may be performed using an appropriate acylation or sulphonation procedure, for example, by treating a compound of formula (I) wherein R^3 is $-NH_2$ with an acetyl or sulphonyl chloride, such as phenylacetyl chloride.

(f) converting a group R^3 which represents halo, such as bromo, into another group R^3 which represents alkyl or aryl, such as phenyl. Such a conversion may be performed using an appropriate alkylation or arylation procedure, for example, by treating a compound of formula (I) wherein R^3 is halo, such as bromo, with a boronic acid, such as phenyl boronic acid, in the presence of a suitable catalyst, such as $PdCl_2(dppf)$.

Alternatively, a group R^3 which represents halo, such as bromo, may be converted into another group R^3 which represents pinacolboronate, using bis pinacolato diboron in the presence of a suitable catalyst, such as $PdCl_2(dppf)$. The resulting pinacolboronate substituent (R^3) may be further converted into another group R^3 which represents aryl or

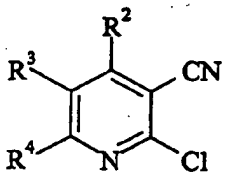
heteroaryl, by treatment with an appropriate aryl or heteroaryl halide, such as phenyl bromide in the presence of a suitable catalyst such as tetrakis(triphenylphosphine)palladium (0).

Suitable conversions of one group R^4 into another group R^4, as in conversion (iii) above, include:

(g) converting a group R^4 which represents aryl substituted by arylalkoxy, such as 4-benzyloxyphenyl, into another group R^4 which represents aryl substituted by –OH, such as 4-hydroxyphenyl. Where R^4 represents aryl substituted by arylmethyloxy such a conversion may be performed using an appropriate hydrogenation procedure, for example, by treating a compound of formula (I) wherein R^3 is aryl substituted by arylalkoxy, such as 4-benzyloxyphenyl, with H_2 in the presence of a suitable catalyst such as 10%Pd/C. Where R^4 represents aryl substituted by arylalkoxy or alkoxy such a conversion may be performed using a suitable ether cleavage reagent such as hydrobromic acid or boron tribromide; and

(h) converting a group R^4 which represents heteroaryl, such as furan-2-yl, into another group R^4 which represents heteroaryl substituted by di-alkylamino, such as 5-dimethylaminofuran-2-yl. Such a conversion may be performed using an appropriate amination procedure, for example, by treating a compound of formula (I) wherein R^4 is an electron rich heteroaryl group with N,N-dimethylmethylene ammonium iodide.

Compounds of formula (II) where R^5 is H may be prepared by reaction of a compound of formula (VIII),



(VIII)

wherein,

R^2, R^3 and R^4 are as defined in relation to formula (I), with hydrazine or a hydrate thereof.

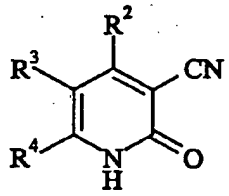
The reaction between the compound of formula (VIII) and hydrazine or a hydrate thereof, is carried out in a suitable solvent at a suitable temperature, generally an elevated

temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Suitable solvents include pyridine and ethanol. Suitable reaction temperatures include those in the range of 60 °C to 220 °C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 1-48 hours. The reaction products are isolated using conventional methods. Typically, the reaction mixture is cooled, the product isolated by filtration, and dried. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products may, if desired, be purified by conventional methods, such as crystallisation, chromatography and trituration.

In a preferred aspect, hydrazine or a hydrate thereof, such as hydrazine hydrate, is added to a stirred solution of the compound of formula (VIII) in pyridine. The reaction mixture is stirred at reflux for 6 hours and cooled. The crude product is isolated by filtration and dried. The crude product may be used without purification.

Certain compounds of formula (II) are believed to be novel and accordingly form a further aspect of the present invention.

Compounds of formula (VIII) may be prepared by reaction of a compound of formula (VIV),



(VIV)

wherein,

R^2, R^3 and R^4 are as defined in relation to formula (I), with a mixture of phosphorus oxychloride and phosphorus pentachloride.

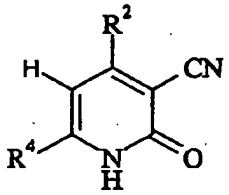
The reaction between the compound of formula (VIV) and a mixture of phosphorus oxychloride and phosphorus pentachloride is carried out at a suitable temperature, generally an elevated temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Suitable reaction temperatures include the reflux temperature of the mixture. Suitable reaction times are those in the range 1-48 hours. The reaction products are isolated using conventional methods. Typically, the

reaction mixture is cooled, and added cautiously to iced water. The solution is then basified with a suitable base such as sodium carbonate and the product isolated by filtration. The product is then washed and dried. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction product may, if desired, be purified by conventional methods, such as crystallisation, chromatography and trituration.

In a preferred aspect, the compound of formula (VIV) is added to a suspension of phosphorus oxychloride and phosphorus pentachloride. The suspension is stirred at reflux for 1 hour, cooled, and cautiously added to iced water. The solution is adjusted to pH 11 with sodium carbonate and the product isolated by filtration, washed with water, and dried to afford the desired compound of formula (VIII). The crude product may be used without purification.

Compounds of formula (VIV) are either commercially available or are prepared by analogy with known conventional literature procedures, for example those disclosed in *Recl. Trav. Chim. Pays-Bas, 1974, 93, 233, J. Med. Chem., 1994*, 37, 3303 or in standard reference texts of synthetic methodology such as *J. March, Advanced Organic Chemistry, 4th Edition, 1992, Wiley Interscience.*

However, compounds of formula (VIV) where R^2 is as defined in relation to formula (I) and R^3 is halo and R^4 is aryl and heteroaryl may be prepared by reaction of a compound of formula (X),



(X)

wherein R^2 is as defined in relation to formula (I) and R^4 is aryl and heteroaryl, with a suitable halogenating agent, such as an N-halosuccinimide.

Compounds of formula (VIV) where R^2 is as defined in relation to formula (I), R^3 is halo and R^4 is aryl and heteroaryl are believed to be novel and accordingly form a further aspect of the present invention.

Certain compounds of formula (X) are believed to be novel and accordingly form a further aspect of the present invention.

Compounds of formula (VII) may be prepared by reaction of a compound of formula (II) with a compound of formula (VI).

Compounds of formula (VII) are believed to be novel and accordingly form a further aspect of the present invention.

Compounds of formulae (I), (II) and (VIV) and (X) may exist as tautomers. The present invention encompasses all tautomeric forms of the compounds of (I), (II) and (VIV)and (X).

As stated above, the compounds of formula (I), or pharmaceutically acceptable salts or solvates thereof, are indicated to be useful as inhibitors of glycogen synthase kinase-3.

The invention therefore provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an inhibitor of GSK-3.

Accordingly, the present invention also provides a method for the treatment of conditions associated with a need for inhibition of GSK-3 such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency, which method comprises the administration of a pharmaceutically

effective, non-toxic amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The present invention further provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an inhibitor of glycogen synthase kinase-3, and especially for use in the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use in the manufacture of a medicament for the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency.

In a further aspect of this invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

Preferably, the compounds of formula (I), or pharmaceutically acceptable salts or solvates thereof, are administered as pharmaceutically acceptable compositions.

Accordingly, the invention also provides a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The active compounds are usually administered as the sole medicament agent but they may be administered in combination with other medicament agents as dictated by the severity and type of disease being treated.

The said combination comprises co-administration of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and an additional medicament agent or the sequential administration of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and the additional medicament agent.

Co-administration includes administration of a pharmaceutical composition which contains both a compound of formula (I), or a pharmaceutically acceptable salto or solvate thereof, and the additional medicament agent or the essentially simultaneous administration of separate pharmaceutical compositions of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and the additional medicament agent.

The compositions of the invention are preferably adapted for oral administration. However, they may be adapted for other modes of administration. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions. In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose. Preferably the composition are in unit dosage form. A unit dose will generally contain from 0.1 to 1000 mg of the active compound.

Generally an effective administered amount of a compound of the invention will depend on the relative efficacy of the compound chosen, the severity of the disorder being treated and the weight of the sufferer. However, active compounds will typically be

administered once or more times a day for example 2, 3 or 4 times daily, with typical total daily doses in the range of from 0.1 to 800 mg/kg/day.

Suitable dose forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed

under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The formulations mentioned herein are carried out using standard methods such as those described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) or the above-mentioned publications.

Suitable methods for preparing and suitable unit dosages for the additional medicament agent, such as the antidiabetic agent mentioned herein include those methods and dosages described or referred to in the above-mentioned reference texts.

GSK-3 Assay

GSK-3 assays used to test the compounds of the invention include the following protocol which is based on the ability of the kinase to phosphorylate a biotinylated 26 mer peptide, Biot- KYRRAAVPPSPSLSRHSSPHQ(S)EDEEE, the sequence of which is derived from the phosphorylation site of glycogen synthase, where (S) is a pre-phosphorylated serine as in glycogen synthase *in vivo* and the three consensus sites for GSK-3 specific phosphorylation are underlined. The phosphorylated biotinylated peptide is then captured onto Streptavidin coated SPA beads (Amersham Technology), where the signal from the ^{33}P is amplified via the scintillant contained in the beads.

Using microtitre plates, GSK-3 was assayed in 50 mM MOPS buffer, pH 7.0, containing 5% glycerol, 0.01% Tween-20, 7.5 mM 2-mercaptoethanol, 10 mM magnesium acetate, 8 uM of the above peptide, and 10 uM [^{33}P]-ATP. After incubation at room temperature, the reaction was stopped by addition of 50 mM EDTA solution containing the Streptavidin coated SPA beads to give a final 0.2 mgs. Following centrifugation, the microtitre plates are counted in a Trilux 1450 microbeta liquid scintillation counter (Wallac). IC_{50} values are generated for each compound by fitting to a four parameter model.

The most potent compounds of the present invention show IC_{50} values in the range of 1 to 500 nM.

No adverse toxicological effects are expected for the compounds of the invention, when administered in accordance with the invention.

The following Descriptions and Examples illustrate the invention, but do not limit it in any way.

Synthetic Method A

Example 1

N-[6-(4-Chlorophenyl-1*H*-pyrazolo[3,4-b]pyridin-3-yl]acetamide

Acetic anhydride (49 mg, 0.445 mmol) was added to a solution of 6-(4-chlorophenyl)-1*H*-pyrazolo[3,4-b]pyridin-3-ylamine (99 mg, 0.40 mmol) in pyridine (0.5 mL). The reaction mixture was stirred at reflux for 16 hours, allowed to cool and treated with 5N hydrochloric acid (5 mL). Solid was filtered off, washed with water and recrystallised from dimethylformamide to afford the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 287/289 ($C_{14}H_{11}ClN_4O$ requires $[M+H]^+$ at m/z 287/289).

^1H NMR δ (DMSO-d_6): 2.13 (3H, s), 7.59 (2H, d), 7.74 (1H, d), 8.19 (2H, d), 8.47 (1H, d), 10.7 (1H, s), 13.2 (1H, br s).

Synthetic Method B

Example 4

1-Ethyl-3-(5-phenyl-1H-pyrazolo[3,4-b]pyridinyl)-urea

To a stirred solution of 5-phenyl-1H-pyrazolo[4,3-b]pyridin-3-ylamine (100 mg, 0.48 mmol) in dry pyridine (5 mL) was added ethyl isocyanate (38 µl, 0.48 mmol). After 18 hours 1N hydrochloric acid (10 mL) was added and the resulting precipitate was filtered to afford the title compound.

MS (APCI +ve): $[M+H]^+$ at m/z 282 ($C_{15}H_{15}N_5O$ requires $[M+H]^+$ at m/z 282).

^1H NMR δ (DMSO-d_6): 1.11-1.19 (3H, t), 3.30-3.37 (2H, m), 7.41-7.45 (1H, m), 7.52-7.56 (2H, m), 7.71-7.73 (2H, m), 8.89 (1H, s), 9.33 (1H, s).

The starting material for Example 4 may be prepared as shown in Descriptions 1 and 2.

Description 1

2-Chloro-5-phenyl-1-nicotinonitrile

2-Oxo-5-phenyl-1,2-dihydropyridine-3-carbonitrile (2.50 g, 12.7 mmol) was added to a suspension of phosphorus oxychloride (1.5 mL) and phosphorus pentachloride (7.35 g) at room temperature. The suspension was then stirred at reflux for 1 hour. The reaction mixture was cooled to room temperature and added cautiously to iced water. The solution was then adjusted to pH 11 with sodium carbonate and the resulting white solid was filtered, washed with water, then dried *in vacuo* to afford the title compound as a solid.

^{1}H NMR δ (DMSO-d6): 8.8 (d, 1H), 8.2 (d, 1H), 7.6-7.5 (m, 5H).

Description 2

5-Phenyl-1*H*-pyrazolo[3,4-b]pyridin-3-ylamine

Hydrazine hydrate (1.42 g, 28 mmol) was added to a stirred solution of 2-chloro-5-phenyl-1-nicotinonitrile (2.45 g, 11.4 mmol) in pyridine (25 mL). The reaction mixture was stirred at reflux for 6 hours, cooled and the resulting solid was filtered and dried *in vacuo*, affording the title compound as a solid.

^{1}H NMR δ (DMSO-d_6): 8.7 (d, 1H), 8.4 (d, 1H), 7.7 (d, 2H), 7.5 (appt, 2H), 7.4 (d, 1H), 5.6 (s, 2H).

<u>Synthetic Method C</u>

Example 9

***N*-(5-Bromo-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-butyramide**

To 5-bromo-1H-pyrazolo[3,4-*b*]pyridin-3-ylamine (100 mg, 0.47 mmol) in pyridine (3 mL) was added butyryl chloride (48 μL, 0.47 mmol) and the solution heated under reflux conditions for 16 hours. The solvent was removed *in vacuo* and then the compound taken up in methanol and run through an SCX cartridge with methanol as the eluant. Product was eluted using 2 normal methanolic ammonia solution. Purification was achieved using silica chromatography (10% methanol in dichloromethane as eluant). Trituration with dichloromethane yielded the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 283/285 ($C_{10}H_{11}ON_4Br$ requires $[M+H]^+$ at m/z 283/285).

^{1}H NMR δ (DMSO-d_6): 0.94 (3H, t), 1.66 (2H, m), 2.39 (2H, t), 8.55 (1H, s), 8.61 (1H, s) 10.74 (1H, s), 13.43 (1H, s).

Synthetic Method C

Example 33

Cyclopropanecarboxylic acid (5-bromo-6-phenyl-1H–pyrazolo[3,4-b]pyridin-3-yl)-amide.

To a stirred solution of 5-bromo-6-phenyl-1H–pyrazolo[3,4-b]pyridin-3-ylamine (1 g, 3.5 mmol) in dry pyridine (20 mL) was added cyclopropyl carbonyl chloride (362 mg, 3.5 mmol). The solution was stirred at reflux for 1 hour and then allowed to cool. The reaction mixture was concentrated and the residue was triturated with dichloromethane/methanol to afford the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 357/359 ($C_{16}H_{13}BrN_4O$ requires $[M+H]^+$ at m/z 357/359).

^{1}H NMR δ (DMSO-d_6): 0.82-0.94 (4H, m), 1.93-2.00 (1H, m), 7.38-7.41 (3H, m), 7.60-7.69 (2H, m), 8.80 (1H, s), 11.15 (1H, s), 13.40 (1H, s).

Descriptions 3-6 illustrate the general synthesis of the parent amines, wherein the R3 substituent is halogen in conjunction with an R4 substituted aryl. The starting material for Example 33 above is prepared analogously. The amine product described in Description 6 is the precursor for Examples 64, 65, 73, 75, 77 and 80.

Description 3

5-Bromo-3-cyano-6-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine

A solution of 3-cyano-6-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine (1.0 g, 4.42 mmol) and N-bromosuccinimide (0.79 g, 4.42 mmol) in dimethylformamide (20 mL) was stirred at reflux for 1 hour, allowed to cool and added to water (100 mL). The solid was filtered, washed successively with water, ethanol and ether and dried under vacuum to afford the title compound as a solid.

MS (APCI -ve): $[M-H]^-$ at m/z 303/305 ($C_{13}H_9N_2O_2$ requires $[M-H]^-$ at m/z 303/305).

^{1}H NMR δ (DMSO-d_6): 12.95 (1H, s), 8.48 (1H, s), 7.52 (2H, d), 7.06 (2H, d), 3.83 (3H, s).

Description 4

5-Bromo-2-chloro-3-cyano-6-(4-methoxyphenyl)pyridine

A solution of 5-bromo-3-cyano-6-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine (1.17 g, 3.83 mmol) in phosphoryl chloride (15 mL) and dimethylformamide (0.5 mL) was stirred at reflux for 18 hours, allowed to cool and added to ice (150 mL).

The mixture was extracted with ethyl acetate (3x100 mL). The combined extracts were dried over magnesium sulphate and concentrated. Purification by column chromatography (20% v/v ethyl acetate in hexane) afforded the title compound as a solid.

^{1}H NMR δ ($CDCl_3$) 8.20 (1H, s), 7.79 (2H, d), 7.01 (2H, d), 3.88 (3H, s).

Description 5

5-Bromo-6-(4-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-3-ylamine

A mixture of 5-bromo-2-chloro-3-cyano-6-(4-methoxyphenyl)pyridine (582 mg, 1.80 mmol), hydrazine hydrate (0.25 mL, 5.15 mmol) and ethanol (8 mL) was stirred at reflux for 3 hours, allowed to cool and concentrated. Purification by column chromatography (5% v/v methanol in dichloromethane) afforded the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 319/321 ($C_{13}H_{11}BrN_4O$ requires $[M+H]^+$ at m/z 319/321).

^{1}H NMR δ (DMSO-d_6): 12.1 (1H, s), 8.50 (1H, s), 7.57 (2H, d), 7.02 (2H, d), 5.67 (2H, s), 3.82 (3H, s).

Description 6

5-Bromo-6-(4-hydroxyphenyl)-1H-pyrazolo[3,4-b]pyridin-3-ylamine

A mixture of 5-bromo-6-(4-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridin-3-ylamine (170 mg, 0.53 mmol), boron tribromide (1M solution in dichloromethane, 4 mL) and dichloromethane (20 mL) was stirred at ambient temperature for 16 hours. Methanol (5 mL) was slowly added and the mixture concentrated. Water (10 mL) was added and the mixture treated to pH 7 with 2M sodium hydroxide solution. The resulting solid was filtered, washed with water and dichloromethane and dried under vacuum to afford the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 305/307 ($C_{12}H_9BrN_4O$ requires $[M+H]^+$ at m/z 305/307).

^{1}H NMR δ (DMSO-d_6) 12.15 (1H, s), 9.77 (1H, s), 8.55 (1H, s), 7.54 (2H, d), 6.90 (2H, d), 5.72 (2H, s).

Where R^4 is 2-thienyl the pyridone precursor is prepared by the method of Description 7

Description 7

2-Oxo-6-thiophen-2-yl-1,2-dihydropyridine-3-carbonitrile

Sodium methoxide (43 g, 800 mmol) was added to a solution of ethyl formate in tetrahydrofuran (200 mL) and diethyl ether (200 mL). A solution of 2-acetyl thiophene (32 g, 300 mmol) in tetrahydrofuran (200 mL) was added dropwise over 1 hour. After the addition was complete the reaction mixture was heated to 40 °C for 3 hours then the solvents were removed by distillation (90 °C). The residue was dissolved in water (400 mL) and acetic acid was added until pH 8 was reached. Cyanoacetamide was added (50 g) and the reaction mixture was heated at reflux for 18 hours. The reaction mixture was cooled, acidified with 2N hydrochloric acid and the resulting solid precipitates were filtered and dried affording the title compound as a solid.

^{1}H NMR δ (DMSO-d_6): 7.00-7.20 (1H, br s), 7.20 (1H, dd), 7.90 (1H, d), 7.90 (1H, dd), 8.10 (1H, d), 12.60-12.90 (1H, br s)

Similarly for compounds where R^3 is a methyl group, the following Descriptions 8-12 illustrate the preparation of the amine intermediate that can be acylated by standard procedures (e.g. Synthetic Method C) to give Examples 54-57, 68, 71 and 74.

Description 8

3-Dimethylamino-1-(4-methoxyphenyl)-2-methylpropenone

A solution of 4'-methoxypropiophenone (16.42 g, 0.1 mol) and N,N-dimethylformamide dimethyl acetal (11.35 g, 0.11 mol) in dry dimethylformamide (100 mL) was heated at 100°C for 24 hours. More dimethylformamide dimethyl acetal (9.29 g, 0.09 mol) was added and the solution was heated for a further 16 hours at 100°C then for 5 hours at 120°C. The solution was evaporated to low volume and the residue was taken up in ethyl acetate (250 mL) and washed with water (x3), brine, dried over magnesium sulphate and

evaporated to an oil. This was triturated with petroleum ether to give the title compound as a solid.

MS (ES +ve): $[M+H]^+$ at m/z 220 ($C_{13}H_{17}NO_2$ requires $[M+H]^+$ at m/z 220).

^1H NMR δ (DMSO-d_6): 2.00 (3H, s), 3.00 (6H, s), 3.78 (3H, s), 6.87 (1H, s), 6.93 (2H, m), 7.30 (2H, m).

Description 9

3-Cyano-5-methyl-6-(4-methoxyphenyl)-2-pyridone

A mixture of 3-dimethylamino-1-(4-methoxyphenyl)-2-methylpropenone (16.35 g, 74.6 mmol), cyanoacetamide (6.27 g, 74.6 mmol) and sodium methoxide (8.05 g, 149 mmol) in dry dimethylformamide (100 mL) was heated at 100°C for 5 hours. The mixture was cooled and poured into water (500 mL). 2N Hydrochloric acid was added to pH 4 and the resulting solid was filtered off and washed with water to give the title compound as a solid.

MS (ES +ve): $[M+H]^+$ at m/z 241 ($C_{14}H_{12}N_2O_2$ requires $[M+H]^+$ at m/z 241).

^1H NMR δ (DMSO-d_6): 1.99 (3H, s), 3.82 (3H, s), 7.05 (2H, m), 7.43 (2H, m). 8.11 (1H, s), 12.40 (1H, s).

Description 10

2-Chloro-3-cyano-5-methyl-6-(4-methoxyphenyl)pyridine

3-Cyano-5-methyl-6-(4-methoxyphenyl)-2-pyridone (13.96 g, 58 mmol) was suspended in phosphoryl chloride (50 mL), dimethylformamide (0.25 mL) added and the mixture heated at reflux for 5 hours. The mixture was cooled and poured with vigorous stirring into ice (500 g). Dichloromethane (400 mL) was added and the mixture was filtered. The layers were separated and the organic layer was washed with water at pH 7 (sodium hydroxide) and brine, dried over magnesium sulphate and evaporated to a solid. This was taken up in dichloromethane and filtered through a bed of silica gel, washing through with more dichloromethane. The filtrate was evaporated and the residue triturated with ether to give the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 259/261 ($C_{14}H_{11}ClN_2O$ requires $[M+H]^+$ at m/z 259/261).

^{1}H NMR δ (DMSO-d_6): 2.40 (3H, s), 3.84 (3H, s), 7.07 (2H, m), 7.62 (2H, m), 8.41 (1H, s).

Description 11

3-Amino-5-methyl-6-(4-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridine

A mixture of 2-chloro-3-cyano-5-methyl-6-(4-methoxyphenyl)pyridine (9.68 g, 37.4 mmol) and hydrazine hydrate (6.74g, 114 mmol) in pyridine (40 mL) was heated at reflux for 7 hours. The mixture was evaporated to dryness and the residue treated with water (100 mL) and the solid broken up well and filtered off to give the title compound as a solid.

MS (ES +ve): $[M+H]^+$ at m/z 255 ($C_{14}H_{14}N_4O$ requires $[M+H]^+$ at m/z 255).

^{1}H NMR δ (DMSO-d_6): 2.34 (3H, s), 3.82 (3H, s), 5.46 (2H, s), 7.01 (2H, m), 7.50 (2H, m), 7.97 (1H, s), 11.75 (1H, s).

Description 12

3-Amino-5-methyl-6-(4-hydroxyphenyl)-1H-pyrazolo[3,4-b]pyridine

3-Amino-5-methyl-6-(4-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridine (2.54 g, 10 mmol) in 48% aqueous hydrobromic acid (50 mL) was heated at reflux overnight. The solution was evaporated to a solid which was dissolved in water (50 mL) and 40% sodium hydroxide solution was added to pH4 then aqueous sodium bicarbonate to pH 7.5. After standing for 15 mins the mixture was filtered to give the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 241 ($C_{13}H_{12}N_4O$ requires $[M+H]^+$ at m/z 241).

^{1}H NMR δ (DMSO-d_6): 2.34 (3H, s), 5.44 (2H, s), 6.84 (2H, m), 7.39 (2H, m), 7.94 (1H, s), 9.60 (1H, s), 11.70 (1H, s).

Synthetic Method C

Example 27

***N*-[3-(2-Methylpropanoylamino)-1H-pyrazolo[3,4-*b*]pyridin-5-yl]-benzamide**

Isobutyryl chloride (105 mg, 0.988 mmol) was added to a solution of N–(3-amino-1H-pyrazolo[3,4-*b*]pyridin-5-yl)-benzamide (250 mg, 0.988 mmol) in hot pyridine. The reaction was stirred at reflux for 55 hours and then the solvent was evaporated *in vacuo*.

The residue was chromatographed on silica (10% methanol/dichloromethane) to yield the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 324 ($C_{17}H_{17}N_5O_2$ requires $[M+H]^+$ at m/z 324).

^1H NMR δ (DMSO-d_6): 1.16 (6H, d), 2.75 (1H, m), 7.55 (2H, t), 7.62 (1H, m), 8.01 (2H, d), 8.65 (1H, s), 8.80 (1H, s), 10.5 (1H, br s), 10.6 (1H, br s), 13.15 (1H, br s).

The starting material for Example 27 is prepared according to Descriptions 13-15 below.

Description 13

5-Amino-2-chloronicotinonitrile

2-Chloro-5-nitronicotinonitrile (Fanta *et al.*, JACS, 1955, 77, 1045), (10 g, 0.054 mol), was suspended in ether (50 mL), and to this solution was added slowly (exotherm) a solution of tin II chloride dihydrate (45 g, 0.199 mol) in concentrated hydrochloric acid (90 mL). The reaction was then stirred until the internal temperature reached 30°C, then diluted with water (200 mL), made strongly basic with 50% sodium hydroxide, cooled and filtered. The solid was washed thoroughly with water, then dried under vacuum at 45°C to yield the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 154 ($C_6H_4ClN_3$ requires $[M+H]^+$ at m/z 154).

^1H NMR δ (DMSO-d6): 6.02 (2H, s), 7.39 (1H, s), 7.96 (1H, s).

Description 14

***N*-(6-Chloro-5-cyano-pyridin-3-yl)-benzamide**

5-Amino-2-chloro-nicotinonitrile (450 mg, 2.93 mmol) was dissolved in dry tetrahydrofuran (10 mL), and to this solution was added dry pyridine (0.26 mL, 3.22 mmol) followed by benzoyl chloride (453 mg, 3.22 mmol). The reaction mixture was heated under reflux for 16 hours under argon. The solvent was then evaporated *in vacuo* and the resulting residue partitioned between ethyl acetate and water and the aqueous layer further extracted with ethyl acetate (x3). The combined organics were washed with brine, then dried over anhydrous magnesium sulfate and evaporated *in vacuo* to yield the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 258 ($C_{13}H_8ClN_3O$ requires $[M+H]^+$ at m/z 258).

^{1}H NMR δ (DMSO-d_6): 7.58 (2H, t), 7.67 (1H, t), 8.13 (2H, d), 8.77 (1H, s), 9.00 (1H, s), 10.85 (1H, s).

Description 15

N-(3-Amino-1H-pyrazolo[3,4-*b*]pyridin-5-yl)-benzamide

N-(6-Chloro-5-cyano-pyridin-3-yl)-benzamide was suspended in ethanol (15 mL) and hydrazine monohydrate (379 mg, 7.58 mmol) was added and the reaction was heated under reflux for 16 hours. The reaction was then filtered hot, and the product was washed thoroughly with ethanol to yield the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 254 ($C_{13}H_{11}N_5O$ requires $[M+H]^+$ at m/z 254).

^{1}H NMR δ (DMSO-d_6): 5.55 (2H, br s), 7.55 (2H, t), 7.61 (1H, t), 7.99 (2H, d), 8.51 (1H, d), 8.54 (1H, d), 10.35 (1H, br s), 11.9 (1H, br s).

Synthetic Method D

Example 10

N-(1H-Pyrazolo[3,4-b]pyridin-3-yl)-butyramide.

To a stirred and degassed solution of N-(5-bromo-1H-pyrazolo[3,4-b]pyridin-3-yl)-butyramide (150 mg, 0.53 mmol) and sodium carbonate (168 mg, 1.59 mmol) in dimethylformamide (1.5 mL), ethanol (0.75 mL) and water (0.75 mL) was added $Pd(PPh_3)_4$ (30 mg, 0.03 mmol). The reaction mixture was stirred at 100°C for 18 hours then allowed to cool. Water was added and the resultant precipitate was filtered and dried. After trituration with dichloromethane the title compound was obtained as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 205 ($C_{10}H_{12}N_4O$ requires $[M+H]^+$ at m/z 205).

^{1}H NMR δ (DMSO-d_6): 0.92-0.98 (3H, t), 1.59-1.73 (2H, m), 2.36-2.42 (2H, q), 7.09-7.14 (1H, m), 8.32-8.37 (1H, m), 8.46-8.49 (1H, m), 1.56 (1H, s), 13.17 (1H, s).

Synthetic Method E

Example 19

[5-(2-Fluorophenyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl]-carbamic acid ethyl ester

5-(2-Fluorophenyl)-1H-pyrazolo[3,4-*b*]pyridin-3-ylamine was dissolved in dry pyridine (10 mL), and to this solution was added 4-(dimethylamino)pyridine (10 mg 0.082 mmol) followed by ethyl chloroformate (95 mg, 0.88 mmol). The reaction was then heated at

reflux for 16 hours under argon. After cooling the pyridine was evaporated *in vacuo* and the residue triturated with dichoromethane to yield a solid. This crude product was chromatographed on silica (5% methanol/dichloromethane) to yield the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 301 ($C_{15}H_{13}FN_4O_2$ requires $[M+H]^+$ at m/z 301).
^1H NMR δ (DMSO-d6): 1.25 (3H, t), 4.17 (2H, q), 7.36 (2H, m), 7.50 (1H, m), 7.60 (1H, t), 8.47 (1H, s), 8.65 (1H, s), 10.2 (1H, s), 13.25 (1H, s).

Synthetic Method F

Example 13

N-[5-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-butyramide

To a stirred and degassed solution of N-(5-bromo-1H-pyrazolo[3,4-b]pyridin-3-yl)-butyramide (5 g, 17.8 mmol), bis pinacolato diboron (5 g, 19.6 mmol) and potassium acetate (5.2 g, 53.4 mmol) in dry dimethylsulfoxide (50 mL) was added $PdCl_2$(dppf) (0.46 g, 0.5 mmol). The solution was heated at 100°C overnight then reaction mixture was allowed to cool. The reaction mixture was filtered through celite, taken up in ethyl acetate (200 mL) and washed with brine (3 x 200 mL). The organic extract was dried (anhydrous magnesium sulfate) and concentrated to afford a brown solid. This solid was triturated with ethyl acetate and filtered to afford the title compound as a solid.
MS (APCI +ve): $[M+H]^+$ at m/z 331 ($C_{16}H_{23}BN_4O_3$ requires $[M+H]^+$ at m/z 331).
^1H NMR δ (DMSO-d_6): 0.84-0.87 (4H, m), 1.33 (12H, s), 1.96-1.99 (1H, m), 8.63-8.64 (1H, d), 8.79 (1H, d), 11.02 (1H, s), 13.28 (1H, s).

Synthetic Method G

Example 14

***N*-(5-Bromo-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-3-methylbutyramide**

To 5-bromo-1H-pyrazolo[3,4-*b*]pyridin-3-ylamine (95 mg, 0.45 mmol) in dimethylformamide (5 mL) was added 3-methylbutyric acid (48 µL, 0.45 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (104 mg, 0.45 mmol) and triethylamine (62 µL, 0.45 mmol). The solution was stirred for 16 hours under ambient conditions. An additional equivalent of the O-(7-azabenzotriazol-1-yl)-

N,N,N',N'-tetramethyluronium hexafluorophosphate and triethylamine was added and the reaction allowed to continue for a further 3 hours. The solvent was removed *in vacuo* and the compound dissolved in methanol and loaded onto an SCX isolute cartridge. After elution with methanol further purification was achieved by preparative HPLC (C18 column, gradient of 10-90% acetonitrile (containing 0.01% trifluoroacetic acid) in water (containing 0.1% trifluoroacetic acid)). The solvent was removed to yield the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 297/299 ($C_{11}H_{12}ON_5Cl$ requires $[M+H]^+$ at m/z 297/299).

^1H NMR δ (DMSO-d_6): 0.96 (6H, d), 2.12 (1H, m), 2.29 (2H, d), 8.55 (1H, s), 8.59 (1H, s) 10.74 (1H, s), 13.43 (1H, s).

Synthetic Method H

Example 18

N-[5-(1-Ethoxyvinyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-butyramide

To a stirred and degassed solution of N-(5-bromo-1H-pyrazolo[3,4-b]pyridin-3-yl)-butyramide (150 mg, 0.53 mmol) and (1-ethoxyvinyl) tributyltin (191 mg, 0.53 mmol) in dry dioxane (5 mL) under argon was added $Pd(PPh_3)_4$ (20 mg, 0.02 mmol). After stirring at reflux for 18 hours the reaction was concentrated in vacuo, taken up in ethyl acetate (20 mL) and washed with water (20 mL). The organic extract was dried (anhydrous magnesium sulfate) and concentrated. The residue was purified by chromatography on silica (0% to 2% methanol/dichloromethane) to afford the title compound as a solid.

MS (APCI -ve): $[M-H]^-$ at m/z 273 ($C_{14}H_{18}N_4O_2$ requires $[M-H]^-$ at m/z 273).

^1H NMR δ (DMSO-d_6): 0.93-0.97 (3H, t), 1.35-1.39 (3H, t), 1.61-1.71 (2H, m), 2.38-2.40 (2H, t), 3.92-3.98 (2H, q), 4.34 (1H, dd), 4.77 (1H, dd), 8.53 (1H, dd), 8.75 (1H, dd), 10.59 (1H, s), 13.25 (1H, s).

Synthetic Method I

Example 20

N-(5-Acetyl-1H-pyrazolo[3,4-b]pyridinyl)-butyramide

To a stirred solution of N-[5-(1-ethoxyvinyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-butyramide (80 mg, 0.29 mmol) in dry methanol (5 mL) was added a solution of 1M hydrochloric

acid in diethyl ether (1mL, 1 mmol). After stirring for 18 hours at 25°C the mixture was concentrated to afford crude 5-acetyl-1H-pyrazolo[3,4-b]pyridin-3-ylamine (40 mg, 0.23 mmol) as a solid. The solid was dissolved in pyridine (2.5 mL) and butyryl chloride was added (24 µl, 0.23 mmol). The reaction mixture was heated at reflux for 5 hours and then cooled to room temperature. The reaction mixture was concentrated and trituration of the crude oil with dichloromethane afforded the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 247 ($C_{12}H_{14}N_4O_2$ requires $[M+H]^+$ at m/z 247).

^1H NMR δ (DMSO-d_6): 0.93-0.97 (3H, t), 1.62-1.72 (2H, m), 2.40-2.44 (2H, t), 2.63 (3H, s), 9.04-9.06 (2H, m), 10.80 (1H, s), 13.53 (1H, s).

<u>Synthetic Method J</u>

Example 21

[5-(3-Fluorophenyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl]-carbamic acid benzyl ester

5-(3-Fluorophenyl)-1 *H*-pyrazolo[3,4-*b*]pyridin-3-ylamine (500 mg, 2.19mmol), was dissolved in dry tetrahydrofuran (75 mL) after vigorous stirring. 4-(Dimethylamino)pyridine (293 mg, 2.40 mmol) was then added followed by benzyl chloroformate (410 mg, 2.40 mmol), and the reaction was stirred at room temperature for 16 hours. The solvent was then evaporated *in vacuo* to yield a crude residue which was chromatographed on silica (solvent gradient 10-50% acetonitrile/dichloromethane) to yield a crude solid, identified as bis-acylated material.

MS (APCI+ve): $[M+H]^+$ at m/z 497 ($C_{28}H_{21}FN_4O_4$ requires $[M+H]^+$ at m/z 497).

The crude material was dissolved in dry piperidine (3 mL) and stirred overnight at room temperature. The piperidine was then evaporated *in vacuo* to yield a crude oil, which was chromatographed on silica (solvent gradient 10-30% acetonitrile/dichloromethane) to yield the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 363 ($C_{20}H_{15}FN_4O_2$ requires $[M+H]^+$ at m/z 363).

^1H NMR δ (DMSO-d_6): 5.21 (2H, s), 7.25 (1H, m), 7.35 (3H, m), 7.43 (2H, m), 7.56 (3H, m), 8.52 (1H, s), 8.83 (1H, s), 10.3 (1H, br s), 13.25 (1H, br s).

Synthetic Method K

Example 22

[5-(3-Fluorophenyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl]-carbamic acid isopropyl ester

5-(3-Fluorophenyl)-1H-pyrazolo[3,4-*b*]pyridin-3-ylamine (200 mg, 0.876mmol) was stirred as a slurry in dry tetrahydrofuran (30 mL), and to the suspension was added 4-(dimethylamino)pyridine (246 mg, 2.01 mmol) followed by isopropyl chloroformate (246 mg, 2.01 mmol), and the reaction was stirred at room temperature for 16 hours. The now homogeneous mixture was evaporated *in vacuo* to yield a crude solid which was chromatographed on silica (10% acetonitrile/dichloromethane) to yield the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 315 ($C_{16}H_{15}FN_4O_2$ requires $[M+H]^+$ at m/z 315).

^1H NMR δ (DMSO-d6): 1.27 (6H, d), 4.95 (1H, m), 7.23 (1H, m), 7.56 (2H, m), 7.60 (1H, d), 8.55 (1H, s), 8.83 (1H, s), 10.1 (1H, s), 13.2 (1H, s).

Synthetic Method L

Example 26

***N*-(5-Amino-1*H*-pyrazolo[3,4-b]pyridin-3-yl)isobutyramide**

N-(5-Nitro-1*H*-pyrazolo[3,4-b]pyridin-3-yl)isobutyramide (Example 23, 0.215 g, 0.863 mmol) was hydrogenated in ethanol (30 mL) with 10% palladium on charcoal (0.12 g) for 4 hours. The catalyst was filtered off using kieselguhr, and the filtrate was evaporated *in vacuo* to give the title compound as a yellow solid.

MS (APCI +ve): $[M+H]^+$ at m/z 220. ($C_{10}H_{13}N_5O$ requires $[M+H]^+$ at m/z 220).

^1H NMR δ (DMSO-d_6): 1.15 (6H, d), 2.70 (1H, m), 5.01 (2H, br s), 7.28 (1H, d), 8.00 (1H, d), 10.20, (1H, s), 12.63 (1H, s).

Synthetic Method M

Example 29

***N*-[5-(Phenylacetylamino)-1H-pyrazolo[3,4-b]pyridin-3-yl]isobutyramide**

N-(5-Amino-1*H*-pyrazolo[3,4-b]pyridin-3-yl)isobutyramide (Example 26, 0.140 g, 0.639 mmol) was stirred in a mixture of dry dichloromethane (10 mL) and dry pyridine (1 mL), and phenylacetyl chloride (0.093 mL, 0.703 mmol) was added dropwise. This mixture was stirred for 6 hours, evaporated to dryness, dissolved in dichloromethane, washed with

saturated sodium hydrogen carbonate solution and brine, dried (anhydrous magnesium sulphate) and evaporated to give a gum. This was purified by silica gel chromatography using (successively) 0%, 2.5%, 5% and 7.5% v/v methanol in dichloromethane as eluent, affording the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 338. ($C_{18}H_{19}N_5O_2$ requires $[M+H]^+$ at m/z 338).
^1H NMR δ (CD_3OD): 1.15 (6H, d), 2.65 (1H, m), 3.62 (2H, s), 7.10-7.30 (7H, m), 8.42 (1H, d), 8.50 (1H, d).

Synthetic Method N

Example 37

Cyclopropanecarboxylic acid (5,6-diphenyl-1H–pyrazolo[3,4-b]pyridin-3-yl)-amide.

To a stirred and degassed solution of cyclopropanecarboxylic acid (5-bromo-6-phenyl-1H–pyrazolo[3,4-b]pyridin-3-yl)-amide (200 mg, 0.56 mmol), phenyl boronic acid (137 mg, 1.12 mmol) and potassium acetate (165 mg, 1.68 mmol) in dimethylformamide (2 mL), ethanol (1 mL) and water (1mL) was added $PdCl_2$(dppf) (20 mg, 0.02 mmol). The reaction mixture was stirred at 100°C for 18 h then the solution was allowed to cool. Water was added and the resulting precipitate was filtered and washed with diethyl ether. This solid was purified by chromatography (30% ethyl acetate/hexane) to afford the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 355 ($C_{22}H_{18}N_4O$ requires $[M+H]^+$ at m/z 355).
^1H NMR δ (DMSO-d_6): 0.82-0.86 (4H, m), 1.92-1.99 (1H, m), 7.13-7.17 (2H, m), 7.23-7.34 (8H, m), 8.40 (1H, s), 11.7 (1H, s), 13.24 (1H, s).

As an alternative to the above Suzuki coupling methodology 5,6-diaryl compounds may be prepared via the pyridone preparation detailed in Descriptions 16 and 17.

Description 16

3-Diethylamino-1-(4-methoxyphenyl)-2-phenylpropenone

Diethylaminostyrene (8.51 g, 50 mmol) and triethylamine (7 mL, 50 mmol) were dissolved in dry toluene(150 mL) and a solution of anisoyl chloride in toluene (150 mL) was added dropwise. The mixture was refluxed overnight, cooled to room temperature and water (200 mL) added. The layers were separated and the organic layer was washed

with water and brine, dried over magnesium sulphate and evaporated to an oil. This was chromatographed on silica gel using dichloromethane-diethyl ether (gradient from 50:1 to 10:1 v/v) as eluent to afford the title compound as an oil.

MS (APCI +ve): $[M+H]^+$ at m/z 241 ($C_{13}H_{12}N_4O$ requires $[M+H]^+$ at m/z 241).

Description 17

3-Cyano-5-phenyl-6-(4-methoxyphenyl)-2-pyridone

A mixture of 3-diethylamino-1-(4-methoxyphenyl)-2-phenylpropenone (5.23 g, 16.9 mmol), cyanoacetamide (1.42 g, 16.9 mmol) and sodium methoxide (1.83 g, 33.8 mmol) in dry dimethylformamide (100 mL) was heated at 100°C for 5 hours. The mixture was cooled and poured into water (250 mL). 2N hydrochloric acid was added to pH4.5 giving an oil which slowly solidified. This was filtered off and washed well with ether to give the title compound as a solid.

MS (APCI -ve): $[M-H]^-$ at m/z 301 ($C_{19}H_{14}N_2O_2$ requires $[M-H]^-$ at m/z 301).

^1H NMR δ (DMSO-d_6): 3.74 (3H, s), 6.86 (2H, d), 7.06 (2H, m), 7.20 (5H, m), 8.19 (1H, s), 12.65 (1H, s).

Synthetic Method O

Example 38

Cyclopropanecarboxylic acid [6-(4-hydroxyphenyl-1H-pyrazolo[3,4-b]pyridin-3-yl]-amide

10% Palladium on carbon (100 mg) was added to a solution of cyclopropanecarboxylic acid [6-(4-benzyloxyphenyl-1H-pyrazolo[3,4-b]pyridin-3-yl]-amide (77 mg, 0.20 mmol) in ethanol (25 mL) and dimethylformamide (10 mL) and the mixture hydrogenated at 50 psi for 60 hours. After removal of the catalyst by filtration and concentration of the filtrate, purification by column chromatography (10% v/v methanol in dichloromethane) afforded the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 295 ($C_{16}H_{14}N_4O_2$ requires $[M+H]^+$ at m/z 295).

^1H NMR δ (DMSO-d_6): 0.86 (4H, m), 1.96 (1H, m), 6.89 (2H, d), 7.59 (1H, d), 8.00 (2H, d), 8.37 (1H, d), 9.83 (1H, s), 10.95 (1H, s), 13.05 (1H, s).

Synthetic Method P

Example 82

N-(5-Bromo-6-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-4-(4-ethylpiperazin-1-yl)-butyramide maleate salt

5-Bromo-6-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-ylamine (0.10 g, 0.346 mmol) was added to a stirred mixture of 4-(4-ethylpiperazin-1-yl)-butyryl chloride hydrochloride salt (0.353 g, 1.38 mmol) in dry pyridine (10 mL) at room temperature under argon and then heated at reflux overnight. Water (10 mL) was added and the solution was evaporated to dryness under reduced pressure. Ethanol (10 mL) was then added and the solution again evaporated to dryness. The residue was redissolved in dimethylformamide (6 mL) and purified by preparative HPLC on a Supelco ABZ+plus column (250 cm by 21.2 mm, 12 μm) using a 10-90% acetonitrile (0.1% trifluoroacetic acid) in water (0.1% trifluoroacetic acid) gradient. A solution of the resulting trifluoroacetate salt in methanol was loaded onto an SCX column and washed with methanol (50 mL). The free base of the product was then eluted with ammonia (2M) in methanol and the solution was evaporated to dryness under reduced pressure. A solution of the resulting free base in methanol (25 mL) was then treated with an equivalent of maleic acid to give the title compound as a solid after evaporation of solvents.

MS (APCI +ve): $[M+H]^+$ at m/z 471 and m/z 473 ($C_{22}H_{27}BrN_6O$ requires $[M+H]^+$ at m/z 471 and m/z 473).

^{1}H NMR δ (MeOH-d_4): 1.26 (3H, t), 1.99 (2H, quintet), 2.58 (2H, t), 2.67 (2H, t), 2.84 (4H, br. app. s), 3.03 (2H, q), 3.18 (4H, br. app. s), 6.26 (2H, s), 7.43-7.51 (3H, m), 7.60-7.68 (2H, m), 8.81 (1H, s).

Synthetic Method Q

Example 119

Cyclopropanecarboxylic acid (5-cyano-6-phenyl-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-amide

Cyclopropanecarboxylic acid (5-iodo-6-phenyl-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-amide (0.100 g, 0.25 mmol) was dissolved in dimethylformamide (5 mL) and treated with copper (I) cyanide (0.034 g, 0.38 mmol). The reaction mixture was heated to reflux for 16 hours and then concentrated *in vacuo*. The product was purified by silica gel

chromatography eluting with dichloromethane/methanol (99:1) to yield the title compound as a solid.

MS (APCI +ve): $[M+H]^+$ at m/z 304. ($C_{17}H_{13}N_5O$ requires $[M+H]^+$ at m/z 304).

^1H NMR δ (DMSO-d_6): 0.90 (4H, m), 1.98 (1H, m), 7.59 (3H, m), 7.87 (2H, m), 9.05 (1H, s), 11.35 (1H, s), 13.81 (1H, s).

Synthetic Method R

Example 164

Cyclopropanecarboxylic acid [5-bromo-6-(5-dimethylaminomethylfuran-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-amide

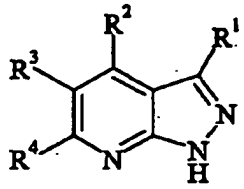
Cyclopropanecarboxylic acid (5-bromo-6-(furan-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-amide (0.300 g, 0.86 mmol) was dissolved in acetic acid (5 mL) and treated with Eschenmoser's salt (N,N-dimethylmethylene ammonium iodide) (0.500 g, 2.6 mmol). The reaction mixture was heated to reflux for 3 hours and then concentrated *in vacuo*. The product was purified by silica gel chromatography eluting with 5% methanol (containing 10% of 0.880 ammonia) in dichloromethane, then applied to a SCX column eluting with methanol first and then ammonia/methanol (10% 0.880 ammonia in methanol) to yield, after evaporation to dryness, the title compound as a solid.

MS (APCI -ve): $[M-H]^-$ at m/z 402/404. ($C_{17}H_{18}BrN_5O_2$ requires $[M-H]^-$ at m/z 402/404).

^1H NMR δ (MeOH-d_4): 0.90 (2H, m), 1.00 (2H, m), 1.90 (1H, m), 2.35 (6H, s), 3.68 (2H, s), 6.54 (1H, d), 7.43 (1H, d), 8.76 (1H, s).

Further Examples of the invention are illustrated in Table 1. The further Examples described herein were prepared by analogy with Synthetic Methods A-R described above.

Table 1



(I)

Ex	Method	R^1	R^2	R^3	R^4	Calculated Mass M	Observed [M+H]+ or [M-H]- or M-
1	A	NHCOMe	H	H	4-Cl-Ph	286.721	287/289
2	A	NHCOMe	H	H	3-CF3-Ph	320.273	321
3	A	NHCOMe	H	H	3,4-diOH-Ph	284.274	285
4	B	NHCONHEt	H	Ph	H	281.32	282
5	B	NHCONH(2-Me-Ph)	H	Ph	H	343.39	344
6	B	NHCONH(2-MeO-Ph)	H	Ph	H	359.39	360
7	B	NHCONH(2-CN-Ph)	H	Ph	H	354.37	355
8	B	NHCONH(2-CO2Me-Ph)	H	Ph	H	387.4	388
9	C	NHCOPr^n	H	Br	H	283.13	283/285
10	D	NHCOPr^n	H	H	H	204.23	205
11	A	N(Et)COPr^n	H	Ph	H	308.383	309
12	E	NHCO2Et	H	Ph	H	282.3	283
13	F	NHCOPr^n	H	Pinacolbo-ronato	H	330.19	331.2
14	G	NHCOBu^t	H	Br	H	297.16	297/299
15	C	NHCO(CH2)4-thiomorpholin-4-yl	H	Br	H	398.33	398/400
16	H	NHCOPr^n	H	CH2CH=CH2	H	244.3	245
17	H	NHCOPr^n	H	CH=CH2	H	230.27	231
18	H	NHCOPr^n	H	C(OEt)=CH2	H	274.32	[M-H]- 273
19	E	NHCO2Et	H	2-F-Ph	H	300.29	301
20	I	NHCOPr^n	H	COMe	H	246.3	247
21	J	NHCO2CH2Ph	H	3-F-Ph	H	362.36	363
22	K	NHCO2Pr^i	H	3-F-Ph	H	314.32	315
23	C	NHCOPr^i	H	NO2	H	249.23	250

24	C	NHCOPr^i	H	NHCOMe	H	261.24	262
25	C	NHCOPr^i	H	NHSO2Me	H	297.34	298
26	L	NHCOPr^i	H	NH2	H	219.25	220
27	C	NHCOPr^i	H	NHCOPh	H	323.35	324
28	C	NHCOPr^i	H	NHCO(2,3-diF-Ph)	H	359.34	360
29	M	NHCOPr^i	H	NHCOCH2Ph	H	337.38	338
30	C	NHCOPr^i	H	NHCOPr^i	H	289.34	290
31	C	NHCOPr^i	H	NHCOCH2OMe	H	291.31	292
32	C	NHCOcyclo-Propyl	H	H	3,4-diOH-Ph	310.312	311
33	C	NHCOcyclo-Propyl	H	Br	Ph	357.21	357/359
34	C	NHCOcyclo-Propyl	H	H	Ph	278.314	279.1
35	C	NHCOcyclo-Propyl	H	H	3,4-OCH2O-Ph	322.323	323
36	C	NHCOcyclo-Propyl	H	H	4-PhCH2O-Ph	384.437	385
37	N	NHCOcyclo-Propyl	H	Ph	Ph	354.411	355.1
38	O	NHCOcyclo-Propyl	H	H	4-OH-Ph	294.313	295
39	N	NHCOcyclo-Propyl	H	3-Pyridyl	Ph	355.399	356
40	C	NHCOcyclo-Propyl	H	H	3-MeO-Ph	308.339	309
41	C	NHCOcyclo-Pentyl	H	H	3-MeO-Ph	336.393	337
42	C	NHCOcyclo-Propyl	H	H	2-MeO-Ph	308.339	309
43	C	NHCOcyclo-Pentyl	H	H	2-MeO-Ph	336.393	337
44	C	NHCOcyclo-Propyl	H	H	3-HO-Ph	294.313	295
45	C	NHCOcyclo-Pentyl	H	H	3-HO-Ph	322.366	323
46	C	NHCOcyclo-Propyl	H	H	2-OH-Ph	294.313	295
47	C	NHCOcyclo-Pentyl	H	H	2-OH-Ph	322.366	323
48	C	NHCO-4-(N-Me-Piperidyl)	H	H	3-OH-Ph	351.408	352
49	C	NHCOcyclo-Pentyl	H	H	4-OH-Ph	322.366	323
50	C	NHCO-4-(N-Me-Piperidyl)	H	H	4-OH-Ph	351.408	352
51	C	NHCOcyclo-Propyl	H	H	4-Pyridyl	279.302	280
52	C	NHCO(CH2)3-(4-Et-piperazin-1-yl)	H	H	3-OH-Ph	408.503	409
53	C	NHCO(CH2)3-(4-Et-piperazin-1-yl)	H	H	4-OH-Ph	408.503	409
54	C	NHCOcyclo-Pentyl	H	Me	4-MeO-Ph	350.42	351
55	C	NHCOcyclo-Propyl	H	Me	4-OH-Ph	308.339	309

56	C	NHCOcyclo-Pentyl	H	Me	4-OH-Ph	336.393	337
57	C	NHCO-4-(N-Me-Piperidyl)	H	Me	4-OH-Ph	365.435	366
58	C	NHCOcyclo-Propyl	H	H	3-Cl-4-OH-Ph	328.758	329/331
59	C	NHCOcyclo-Pentyl	H	H	3-Cl-4-OH-Ph	356.811	357/359
60	C	NHCOcyclo-Propyl	H	H	3-Br-4-OH-Ph	373.209	373/375
61	C	NHCO-4-(N-Me-Piperidyl)	H	H	3-Cl-4-OH-Ph	385.853	386/388
62	C	NHCOcyclo-Propyl	H	Ph	4-OH-Ph	370.41	371
63	C	NHCOcyclo-Pentyl	H	Ph	4-OH-Ph	398.464	399
64	C	NHCOcyclo-Propyl	H	Br	4-OH-Ph	373.209	373/375
65	C	NHCOcyclo-Pentyl	H	Br	4-OH-Ph	401.262	401/403
66	C	NHCO-4-(N-Me-Piperidyl)	H	Ph	4-OH-Ph	427.505	428
67	C	NHCOcyclo-Propyl	H	Cl	4-OH-Ph	328.758	329/331
68	C	NHCOPr^i	H	Me	4-OH-Ph	310.355	311
69	C	NHCOPr^i	H	H	3-MeO-Ph	310.355	311
70	C	NHCO-4-(N-Me-Piperidyl)	H	H	3-MeO-Ph	365.435	366
71	C	NHCO(CH2)3-NMe2	H	Me	4-OH-Ph	353.424	354
72	C	NHCO(CH2)3-NMe2	H	H	3-MeO-Ph	353.424	354
73	C	NHCOPr^i	H	Br	4-OH-Ph	375.224	375/377
74	C	NHCO(CH2)3-(4-Et-piperazin-1-yl)	H	Me	4-OH-Ph	422.53	423
75	C	NHCO(CH2)3-(4-Et-piperazin-1-yl)	H	Br	4-OH-Ph	487.399	487/489
76	C	NHCOcyclo-Pentyl	H	H	4-Pyridyl	307.355	308
77	C	NHCO(CH2)3-NMe2	H	Br	4-OH-Ph	418.293	418/420
78	C	NHCOcyclo-Pentyl	H	Br	Ph	385.263	385/387
79	C	NHCOcyclo-Pentyl	H	Cl	4-Pyridyl	341.8	342/344
80	C	NHCO-4-(N-Me-Piperidyl)	H	Br	4-OH-Ph	430.304	430/432
81	P	NHCO(CH2)3-NMe2	H	Br	Ph	402.294	402/404
82	P	NHCO(CH2)3-(4-Et-piperazin-1-yl)	H	Br	Ph	471.4	471/473
83	C	NHCO(CH2)3-(4-Et-piperazin-1-yl)	H	H	2-OH-Ph	408.503	409
84	C	NHCO-4-(N-Me-Piperidyl)	H	H	2-OH-Ph	351.408	352

85	C	NHCO(CH2)3-NMe2	H	H	2-OH-Ph	339.397	340
86	C	NHCOPr^{i}	H	H	2-OH-Ph	296.328	297
87	P	NHCO-4-(N-Me-Piperidyl)	H	Br	Ph	414.305	414/416
88	C	NHCOcyclo-Pentyl	H	Br	2-OH-Ph	401.262	401/403
89	C	NHCOPr^{i}	H	Br	2-OH-Ph	375.224	375/377
90	C	NHCOcyclo-Propyl	H	Br	3-MeO-Ph	387.235	387/389
91	C	NHCOPr^{i}	H	Br	3-MeO-Ph	389.251	389/391
92	C	NHCOcyclo-Pentyl	H	Br	3-MeO-Ph	415.289	415/417
93	C	NHCO(CH2)3-(4-Et-piperazin-1-yl)	H	Cl	2-OH-Ph	442.948	443/445
94	C	NHCO-4-(N-Me-Piperidyl)	H	Br	3-MeO-Ph	444.331	444/446
95	C	NHCOcyclo-Propyl	H	Cl	2-OH-Ph	328.758	329/331
96	C	NHCOcyclo-Propyl	H	Cl	Ph	312.759	313/315
97	C	NHCOcyclo-Propyl	H	Br	2-OH-Ph	373.209	373/375
98	C	NHCO(CH2)3-(4-Et-piperazin-1-yl)	H	Br	3-MeO-Ph	501.426	501/503
99	C	NHCOcyclo-Propyl	H	Br	2-Thienyl	363.238	363/365
100	C	NHCOcyclo-Propyl	H	I	Ph	404.206	405
101	C	NHCO(CH2)3-(4-Et-piperazin-1-yl)	H	H	3-MeO-Ph	422.53	423
102	C	NHCO-4-(N-Me-Piperidyl)	H	Cl	Ph	369.854	370/372
103	C	NHCO(CH2)3-(4-Et-piperazin-1-yl)	H	Cl	Ph	426.949	427/429
104	C	NHCOcyclo-Propyl	H	Cl	3-MeO-Ph	342.784	343/345
105	C	NHCO-4-(N-Me-Piperidyl)	H	Cl	2-OH-Ph	385.853	386/388
106	C	NHCO(CH2)3-(4-Et-piperazin-1-yl)	H	Br	2-Thienyl	477.428	477/479
107	C	NHCO(CH2)3-NMe2	H	Cl	3-MeO-Ph	387.869	388/390
108	C	NHCO-4-(N-Me-Piperidyl)	H	Br	2-Thienyl	420.333	420/422
109	C	NHCO(CH2)3-NMe2	H	Cl	Ph	357.843	358/360
110	C	NHCO-4-(N-((CH2)2OMe)-Piperidyl)	H	Br	Ph	458.358	458/460
111	C	NHCOCH2O(CH2)2OMe	H	Br	Ph	405.25	405/407
112	C	NHCO-4-(N-Me-Piperidyl)	H	I	Ph	461.301	462
113	C	NHCOcyclo-Propyl	H	Me	2-MeO-Ph	322.366	323

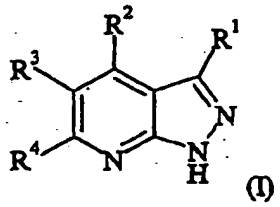
114	C	NHCOCH2OMe	H	Br	Ph	361.198	361/363
115	C	NHCO(CH2)3-NMe2	H	I	Ph	449.29	450
116	C	NHCOCH(Me)(CH2)2-(4-Et-piperazin-1-yl)	H	Br	Ph	485.427	485/487
117	C	NHCO-[6-(3-Pyridyl)-pyrid-3-yl]	H	Br	Ph	471.316	471/473
118	C	NHCO(CH2)3-(4-Et-piperazin-1-yl)	H	I	Ph	518.396	[M-H]- 517
119	Q	NHCOcyclo-Propyl	H	CN	Ph	303.324	304
120	C	NHCO-[4-(CH2(pyrrolidin-1-yl)-Ph]	H	Br	Ph	476.376	476/478
121	C	NHCO-[3-(pyrid-2-yl)-Ph]	H	Br	Ph	470.328	[M-H]- 468/470
122	C	NHCO-[4-(CH2(pyrrolidin-1-yl)-Ph]	H	Cl	Ph	431.925	432/434
123	C	NHCOCH2(N-CH2Ph-Piperidin-4-yl)	H	Br	Ph	504.429	504/506
124	C	NHCOCH2(N-(CH2)2OMe-Piperidin-4-yl)	H	Br	Ph	472.384	472/474
125	P	NHCO(CH2)2(6-Me-Pyridin-3-yl)	H	Br	Ph	436.311	436/438
126	P	NHCO-3-(N-CH2Ph-Pyrrolidinyl)	H	Br	Ph	476.376	476/478
127	C	NHCOCH2(N-(CH2)2OPh-Piperidin-4-yl)	H	Br	Ph	534.455	534/536
128	C	NHCOCH2(N-Et-Piperidin-4-yl)	H	Br	2-Thienyl	448.387	448/450
129	C	NHCOCH2(N-(CH2)2OMe-Piperidin-4-yl)	H	Br	2-Thienyl	478.413	478/480
130	C	NHCOcyclo-Propyl	H	Br	2-Furyl	347.171	347/349
131	C	NHCOCH2(N-CH2Ph-Piperidin-4-yl)	H	Br	2-Thienyl	510.458	510/512
132	C	NHCO(CH2)3-(4-Et-piperazin-1-yl)	H	Br	2-Furyl	461.361	461/463
133	C	NHCOcyclo-Propyl	H	H	3-CN-Ph	303.324	304
134	C	NHCO(CH2)2-morpholin-4-yl	H	Br	2-Furyl	420.265	420/422

135	C	NHCO(CH2)3-NMe2	H	Br	2-Furyl	392.255	392/394
136	C	NHCOCH2(N-(CH2)2OMe-Piperidin-4-yl)	H	Br	2-Furyl	462.346	462/464
137	C	NHCOCH2(N-Et-Piperidin-4-yl)	H	Br	2-Furyl	432.32	432/434
138	C	NHCOCH2NMe2	H	Br	2-Furyl	364.202	364/366
139	C	NHCO-3-(N-CH2Ph-Pyrrolidinyl)	H	Br	2-Furyl	466.337	466/468
140	C	NHCO-4-(N-(CH2)2OEt-Piperidyl)	H	Br	2-Furyl	462.346	462/464
141	C	NHCO-4-(N-Me-Piperidyl)	H	Br	2-Furyl	404.266	404/406
142	C	NHCOcyclo-Propyl	H	Br	2-Thiazolyl	364.226	[M-H]-362/364
143	P	NHCO-[4-(CH2(piperidin-1-yl))-Ph]	H	Br	2-Thienyl	496.431	496/498
144	C	NHCO-[4-(CH2(pyrrolidin-1-yl))-Ph]	H	Br	2-Furyl	466.337	466/468
145	C	NHCOcyclo-Propyl	H	Br	5-Me-Furan-2-yl	361.198	361/363
146	C	NHCO-[4-(CH2(pyrrolidin-1-yl))-Ph]	H	Br	2-Thienyl	482.404	482/484
147	C	NHCOcyclo-Pentyl	H	Br	2-Thiazolyl	392.28	392/394
148	C	NHCO-4-(N-Me-Piperidyl)	H	Br	2-Thiazolyl	421.321	421/423
149	C	NHCOCH2(N-Et-Piperidin-4-yl)	H	Br	2-Thiazolyl	449.375	449/451
150	P	NHCO-[4-(CH2NEt2)-Ph]	H	Br	2-Thienyl	484.42	484/486
151	P	NHCO-[4-(CH2(pyrrolidin-1-yl))-Ph]	H	Br	2-Thiazolyl	483.392	483/485
152	P	NHCO(CH2)3-(pyrrolidin-1-yl)	H	Br	Ph	428.332	428/430
153	C	NHCOcyclo-Pentyl	H	Br	5-Me-Furan-2-yl	389.251	389/391
154	C	NHCOcyclo-Pentyl	H	Br	2-Thienyl	391.292	391/393
155	C	NHCOCH2(N-	H	Br	2-Furyl	524.416	524/526

		(CH2)2OPh-Piperidin-4-yl)					
156	P	NHCO(CH2)2(6-Me-Pyridin-3-yl)	H	Br	2-Thiazolyl	443.327	443/445
157	P	NHCO(CH2)3-(4-Et-piperazin-1-yl)	H	Br	2-Thiazolyl	478.417	478/480
158	C	NHCOcyclo-Propyl	H	H	2-Furyl	268.275	269
159	C	NHCOcyclo-Propyl	H	H	cyclo-Propyl	242.281	243
160	C	NHCOCH2(N-(CH2)2OPh-Piperidin-4-yl)	H	Br	2-Thienyl	540.483	540/542
161	C	NHCOcyclo-Propyl	H	PhS	Ph	386.477	387
162	P	NHCO-3-(N-CH2Ph-Pyrrolidinyl)	H	Br	2-Thiazolyl	483.392	483/485
163	C	NHCOCH2(N-Et-Piperidin-4-yl)	H	Br	5-Me-Furan-2-yl	446.347	446/448
164	R	NHCOcyclo-Propyl	H	Br	5-(CH2NMe2)-Furan-2-yl	404.266	[M-H]-402/404
165	C	NHCOcyclo-Pentyl	H	Br	2-Furyl	375.224	375/377
166	P	NHCO(CH2)3-(4-Et-piperazin-1-yl)	H	Br	5-Me-Furan-2-yl	475.388	475/477
167	P	NHCO-3-(N-CH2Ph-Pyrrolidinyl)	H	Br	5-Me-Furan-2-yl	480.364	480/482
168	P	NHCO-[4-(CH2(pyrrolidin-1-yl))-Ph]	H	Br	5-Me-Furan-2-yl	480.364	480/482
169	P	NHCO(CH2)2(6-Me-Pyridin-3-yl)	H	Br	5-Me-Furan-2-yl	440.299	440/442
170	C	NHCOcyclo-Propyl	H	CO2Et	Ph	350.376	351
171	C	NHCOcyclo-Pentyl	H	H	cyclo-Propyl	270.334	271
172	R	NHCOcyclo-Pentyl	H	Br	5-(CH2NMe2)-Furan-2-yl	432.32	[M-H]-430/432
173	C	NHCOCH2(N-CH2Ph-Piperidin-4-yl)	H	Br	5-Me-Furan-2-yl	508.417	508/510
174	C	NHCOcyclo-Propyl	H	CONH(CH2)2NMe2	Ph	392.461	393
175	P	NHCO-3-(N-CH2Ph-Pyrrolidinyl)	H	Br	2-Thienyl	482.404	482/484

Claims

1. A compound of formula (I),



(I)

or a salt thereof, or a solvate thereof, wherein,

R^1 is $-NR^5COR^6$, $-NHCONHR^7$ or $-NHCO_2R^8$;

R^2 is H;

R^3 is H, halo, -CN, $-NO_2$, $-NH_2$, alkyl, alkenyl, $-C(OR^{10})=CHR^{13}$, $-NHCOR^{11}$, $-NHSO_2R^{12}$, $-CO_2R^{13}$, $-COCH_2R^{13}$, $-B(OR^{14})_2$, $-CONHR^{15}$, -SPh, heteroaryl or aryl wherein the aryl group may be optionally substituted by one or more halo substituents;

R^4 is H, cycloC_{3-8} alkyl, heterocyclyl, heteroaryl wherein the heteroaryl group may be optionally substituted by alkyl and di-alkylaminoalkyl; or aryl wherein the aryl group may be optionally substituted by one or more groups selected from halo, -OH, $-CF_3$, -CN, alkoxy and arylalkoxy, or may be fused to a heterocyclic ring to form a bicyclic group;

R^5 is H or alkyl;

R^6 is alkyl, alkenyl, cycloC_{3-8} alkyl, cycloC_{3-8} alkenyl, di-alkylaminoalkyl, arylalkyl, arylalkenyl, heterocyclyl wherein the heterocyclyl group may be optionally substituted by one or more groups selected from alkyl, arylalkyl and alkoxyalkyl; heterocyclylalkyl wherein the heterocyclyl may be optionally substituted by one or more groups selected from alkoxyalkyl, aryloxyalkyl, arylalkyl and alkyl; heteroarylalkyl wherein the heteroaryl may be optionally substituted by one or more groups selected from alkyl; heteroaryl wherein the heteroaryl may be optionally substituted by one or more groups selected from aryl and heteroaryl; aryl wherein the aryl group may be optionally substituted by heterocyclylalkyl and di-alkylaminoalkyl; alkoxyalkyl wherein the alkoxy group may be optionally substituted by alkoxy;

R^7 is alkyl or aryl wherein the aryl group may be optionally substituted by one or more groups selected from alkyl, alkoxy, -CN and $-CO_2R^9$;

R^8 is alkyl or arylalkyl; and

R^9 is alkyl;

R^{10} is alkyl;

R^{11} is alkyl, alkoxyalkyl, arylalkyl or aryl wherein the aryl group may be optionally substituted by one or more groups selected from halo; and

R^{12} is alkyl;

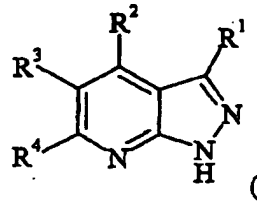
R^{13} is alkyl;

R^{14} is alkyl or two R^{14} groups together form a ring system which may be further substituted by one or more alkyl group(s);

R^{15} is di-alkylaminoalkyl;

with the proviso that when R^1 is $-NR^5COR^6$ wherein R^5 is H and R^6 is as hereinbefore defined, and R^2 and R^4 are H then R^3 is selected from H, halo, -CN, $-NO_2$, $-NH_2$, alkyl, alkenyl, $-C(OR^{10})=CHR^{13}$, $-NHCOR^{11}$, $-NHSO_2R^{12}$, $-CO_2R^{13}$, $-COCH_2R^{13}$, $-CONHR^{15}$ or –SPh.

2. A compound of formula (I), as claimed in claim 1, of formula (IA),



(IA)

or a salt thereof, or a solvate thereof, wherein,

R^1 is $-NR^5COR^6$, $-NHCONHR^7$ or $-NHCO_2R^8$;

R^2 is H;

R^3 is H, halo, -CN, $-NO_2$, $-NH_2$, alkyl, alkenyl, $-C(OR^{10})=CHR^{13}$, $-NHCOR^{11}$, $-NHSO_2R^{12}$, $-CO_2R^{13}$, $-COCH_2R^{13}$, $-B(OR^{14})_2$, $-CONHR^{15}$, -SPh, heteroaryl or aryl wherein the aryl group may be optionally substituted by one or more halo substituents;

R^4 is H, cycloC_{3-8} alkyl, heterocyclyl, heteroaryl wherein the heteroaryl group may be optionally substituted by alkyl and di-alkylaminoalkyl; or aryl wherein the aryl group may

be optionally substituted by one or more groups selected from halo, -OH, -CF_3, -CN, alkoxy and arylalkoxy, or may be fused to a heterocyclic ring to form a bicyclic group;

R^5 is H or alkyl;

R^6 is alkyl, cycloC_{3-8} alkyl, di-alkylaminoalkyl, heterocyclyl wherein the heterocyclyl group may be optionally substituted by one or more groups selected from alkyl, arylalkyl and alkoxyalkyl; heterocyclylalkyl wherein the heterocyclyl may be optionally substituted by one or more groups selected from alkoxyalkyl, aryloxyalkyl, arylalkyl and alkyl; heteroarylalkyl wherein the heteroaryl may be optionally substituted by one or more groups selected from alkyl; heteroaryl wherein the heteroaryl may be optionally substituted by one or more groups selected from aryl and heteroaryl; aryl wherein the aryl group may be optionally substituted by heterocyclylalkyl and di-alkylaminoalkyl; alkoxyalkyl wherein the alkoxy group may be optionally substituted by alkoxy;

R^7 is alkyl or aryl wherein the aryl group may be optionally substituted by one or more groups selected from alkyl, alkoxy, -CN and CO_2R^9;

R^8 is alkyl or arylalkyl;

R^9 is alkyl;

R^{10} is alkyl;

R^{11} is alkyl, alkoxyalkyl, arylalkyl or aryl wherein the aryl group may be optionally substituted by one or more groups selected from halo; and

R^{12} is alkyl;

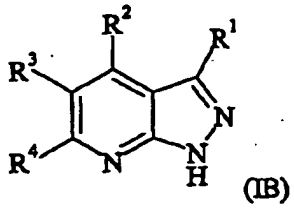
R^{13} is alkyl;

R^{14} is alkyl or two R^{14} groups together form a ring system which may be further substituted by one or more alkyl group(s);

R^{15} is di-alkylaminoalkyl;

with the proviso that when R^1 is $-NR^5COR^6$ wherein R^5 is H and R^6 is as hereinbefore defined, and R^2 and R^4 are H then R^3 is selected from H, halo, -CN, -NO_2, -NH_2, alkyl, alkenyl, -$C(OR^{10})$=CHR^{13}, -$NHCOR^{11}$, -$NHSO_2R^{12}$, -CO_2R^{13},-$COCH_2R^{13}$ -$CONHR^{15}$ or –SPh.

3. A compound of formula (I), as claimed in claim 1, of formula (IB),



(IB)

or a salt thereof, or a solvate thereof, wherein,

R^1 is –NHCOMe, -NHCOPr^n, -NHCOPr^i, -N(Et)COPr^n, -NHCOBu^s, -NHCO$(CH_2)_4$-thiomorpholin-4-yl, -NHCOcyclo-Propyl, -NHCOcyclo-Pentyl, -NHCO-4-(N-Me-Piperidyl), -NHCO$(CH_2)_3$-(4-Et-Piperazin-1-yl), -NHCO$(CH_2)_3NMe_2$, -NHCONHEt, -NHCONH(2-Me-Ph), -NHCONH(2-MeO-Ph), -NHCONH(2-CN-Ph), -NHCONH(2-CO_2Me-Ph), -NHCO$_2$Et, -NHCO$_2$Pr^i, -NHCO$_2CH_2$Ph, NHCO$(CH_2)_2$(6-Me-Pyridin-3-yl), NHCO-[3-(pyrid-2-yl)-Ph], NHCO-[4-(CH_2(pyrrolidin-1-yl)-Ph], NHCO-[6-(3-Pyridyl)-pyrid-3-yl], NHCO-3-(N-CH_2Ph-Pyrrolidinyl), NHCO-4-(N-((CH$_2$)$_2$OMe)-Piperidyl), NHCOCH(Me)$(CH_2)_2$-(4-Et-piperazin-1-yl), NHCOCH$_2$(N-(CH$_2$)$_2$OMe-Piperidin-4-yl), NHCOCH$_2$(N-(CH$_2$)$_2$OPh-Piperidin-4-yl), NHCOCH$_2$(N-CH$_2$Ph-Piperidin-4-yl), NHCOCH$_2$(N-Et-Piperidin-4-yl), NHCOCH$_2$O(CH$_2$)$_2$OMe, NHCOCH$_2$OMe, -NHCO$(CH_2)_2$-morpholin-4-yl, -NHCO$(CH_2)_3$(pyrrolidin-1-yl), -NHCO-[4-(CH_2(piperidin-1-yl)-Ph], -NHCO-[4-(CH_2NEt_2)-Ph], -NHCO-4-(N-$(CH_2)_2$OEt-Piperidyl) and -NHCOCH$_2$NMe$_2$;

R^2 is H;

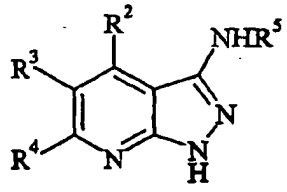
R^3 is H, methyl, phenyl, bromo, chloro, iodo, cyano, pinacolboronato, -$CH_2CH=CH_2$, -$CH=CH_2$, -C(OEt)=CH_2, 2-fluorophenyl, -COMe, 3-fluorophenyl, -NO_2, -NHCOMe, -NHCOPr^i, -$NHSO_2$Me, -NH_2, -NHCOPh, -NHCO(2,3-difluorophenyl), -NHCOCH$_2$Ph, -NHCOCH$_2$OMe, 3-pyridyl, -CO_2Et, -CONH$(CH_2)_2NMe_2$, and -SPh;

R^4 is H, phenyl, 4-chlorophenyl, 3-trifluoromethylphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3,4-dihydroxyphenyl, 3,4-methylenedioxyphenyl, 4-benzyloxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-pyridyl, 3-chloro-4-hydroxyphenyl, 3-bromo-4-hydroxyphenyl and 2-thienyl, 2-furyl 2-thiazolyl, 3-CN-Ph, 5-(CH_2NMe_2)-Furan-2-yl, 5-Me-Furan-2-yl and cyclopropyl;

with the proviso that when R^1 is -NHCOMe, -NHCOPr^n, -NHCOPr^i, -NHCOBu^s, -NHCO$(CH_2)_4$-thiomorpholin-4-yl, -NHCOcyclo-Propyl, -NHCOcyclo-Pentyl, -NHCO-4-(N-Me-Piperidyl), -NHCO$(CH_2)_3$-(4-Et-Piperazin-1-yl), -NHCO$(CH_2)_3NMe_2$, NHCO$(CH_2)_2$(6-Me-Pyridin-3-yl), NHCO-[3-(pyrid-2-yl)-Ph], NHCO-[4-(CH_2(pyrrolidin-1-yl)-Ph], NHCO-[6-(3-Pyridyl)-pyrid-3-yl], NHCO-3-(N-CH_2Ph-Pyrrolidinyl), NHCO-4-(N-(($CH_2)_2$OMe)-Piperidyl), NHCOCH(Me)$(CH_2)_2$-(4-Et-piperazin-1-yl), NHCOCH$_2$(N-$(CH_2)_2$OMe-Piperidin-4-yl), NHCOCH$_2$(N-$(CH_2)_2$OPh-Piperidin-4-yl), NHCOCH$_2$(N-CH_2Ph-Piperidin-4-yl), NHCOCH$_2$(N-Et-Piperidin-4-yl), NHCOCH$_2$O$(CH_2)_2$OMe, NHCOCH$_2$OMe, -NHCO$(CH_2)_2$-morpholin-4-yl, -NHCO$(CH_2)_3$(pyrrolidin-1-yl), -NHCO-[4-(CH_2(piperidin-1-yl)-Ph], -NHCO-[4-(CH_2NEt_2)-Ph], -NHCO-4-(N-$(CH_2)_2$OEt-Piperidyl) and -NHCOCH$_2$NMe$_2$; and R^2 and R^4 are H, then R^3 is selected from H, methyl, bromo, chloro, iodo, cyano, -$CH_2CH=CH_2$, -CH=CH$_2$, -C(OEt)=CH$_2$, -COMe, -NO$_2$, -NHCOMe, -NHCOPr^i, -$NHSO_2Me$, -NH$_2$, -NHCOPh, -NHCO(2,3-difluorophenyl), -NHCOCH$_2$Ph - NHCOCH$_2$OMe, CO_2Et, CONH$(CH_2)_2NMe_2$, and –SPh.

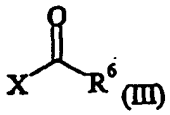
4. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, substantially as hereinbefore described with reference to any one of the Examples.

5. A process for the preparation of a compound of formula (I) wherein R^1 is –NR^5COR^6 and wherein R^2, R^3, R^4, R^5 and R^6 are as hereinbefore defined, or a salt and/or solvate thereof, which process comprises reacting a compound of formula (II),



(II)

wherein R^2, R^3, R^4 and R^5 are as defined in relation to formula (I) with a compound of formula (III),



(III)

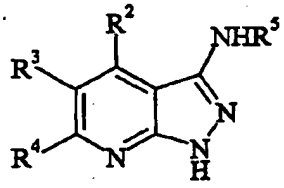
wherein R^6 is as defined in relation to formula (I) and X is a suitable leaving group and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate derivative of the compound so formed.

6. A process for the preparation of a compound of formula (I) wherein R^1 is – $NHCONHR^7$ and wherein R^2, R^3, R^4 and R^7 are as hereinbefore defined, or a salt and/or solvate thereof, which process comprises reacting a compound of formula (II),



(II)

wherein R^2, R^3, R^4 are as defined in relation to formula (I) and R^5 is H, with a compound of formula (V),

$$R^7—NCO \quad (V)$$

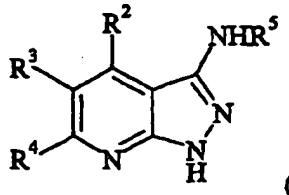
wherein R^7 is as defined in relation to formula (I) and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

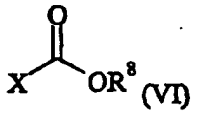
(iii) preparing an appropriate derivative of the compound so formed.

7. A process for the preparation of a compound of formula (I) wherein R^1 is – $NHCO_2R^8$ and wherein R^2, R^3, R^4 and R^8 are as hereinbefore defined, or a salt and/or solvate thereof, which process comprises reacting a compound of formula (II),



(II)

wherein R^2, R^3, R^4 are as defined in relation to formula (I) and R^5 is H, with a compound of formula (VI),



(VI)

wherein R^8 is as defined in relation to formula (I) and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate derivative of the compound so formed.

8. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, and a pharmaceutically acceptable carrier.

9. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, for use as an inhibitor of GSK-3.

10. A method for the treatment of conditions associated with a need for inhibition of GSK-3 such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion

of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency, which method comprises the administration of a pharmaceutically effective, non-toxic amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1.

11. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, for use in the manufacture of a medicament for the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency.

INTERNATIONAL SEARCH REPORT

Interna I Application No
PCT/GB 03/00576

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/4365 A61P25/00 A61P3/10 C07F5/02
A61K31/69 //(C07D471/04,231:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 81345 A (WELFIDE) 1 November 2001 (2001-11-01) abstract	1,10
X	KORBONITS D ET AL: "Ring transformation of 3-(2-aminoaryl)-1,2,4-oxadiazoles into 3-acylaminoindazoles;extension of the Boulton-Katritzy scheme" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, CHEMICAL SOCIETY. LETCHWORTH, GB, vol. 1, no. 3, 1982, pages 759-766, XP002221091 ISSN: 0300-922X table 3, compounds 6.1 and 6.2	1

-/—

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 May 2003	19/05/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern I Application No
PCT/GB 03/00576

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 24694 A (SMITHKLINE BEECHAM) 28 March 2002 (2002-03-28) cited in the application page 33, lines 10-18; page 34, lines 24-38 claims 1,14	1 1,10
P,A	WO 02 088078 A (VERTEX PHARMA) 7 November 2002 (2002-11-07) claims 1,12	1,10
P,A	WO 02 50073 A (SMITHKLINE BEECHAM) 27 June 2002 (2002-06-27) claims 1,14	1,10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/00576

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern Application No
PCT/GB 03/00576

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0181345 A	01-11-2001	AU 4878601 A	07-11-2001
		WO 0181345 A1	01-11-2001
WO 0224694 A	28-03-2002	AU 8789801 A	02-04-2002
		WO 0224694 A1	28-03-2002
WO 02088078 A	07-11-2002	WO 02088078 A2	07-11-2002
WO 0250073 A	27-06-2002	AU 2229302 A	01-07-2002
		WO 0250073 A1	27-06-2002